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# BRITISH MEDICAL JOURNAL

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SATURDAY AUGUST 5 1944

## TABLE OF CONTENTS

**Penicillin: A Survey** Sir H. W. FLOREY, M.B., F.R.S. ..... 169

**Penicillin in Acute Empyema**
E. C. B. BUTLER, F.R.C.S., K. M. A. PERRY, M.D., and F. C. O. VALENTINE, M.R.C.P. ..... 171

**Penicillin in Ophthalmology** J. G. MILNER, F.R.C.S. ..... 175

**Penicillin and Sulphonamides in Infantile Gastro-enteritis**
ELIZABETH BURNS, M.B., and W. GUNN, M.B. ..... 178

**Severe Haemolytic Transfusion Reaction due to the Rh Factor**
A. BECK, M.D., C. V. HARRISON, M.D., and J. M. OWEN, M.B. ..... 180

### MEDICAL MEMORANDA

Treatment of Cerebral Malaria. J. M. ROGAN, M.D. ..... 181
Two Cases of Snake-bite. B. E. A. BATT, M.B. ..... 181
Spontaneous Expulsion through Rectum of a Kocher Forceps left in Abdomen 14 Months. ILHAMI AKCAKOYUNLU, M.D. ..... 182

### GENERAL ARTICLES AND NEWS

**Registration of Specialists** ..... 188
BEIT MEMORIAL FELLOWSHIPS ..... 189
SCIENCE FELLOWSHIPS FOR BRITISH UNIVERSITIES ..... 189
INSTITUTE OF OPHTHALMOLOGY ..... 189
THE SERVICES ..... 196
UNIVERSITIES AND COLLEGES ..... 198
MEDICAL NOTES IN PARLIAMENT ..... 196
MEDICAL NEWS ..... 197

### REVIEWS

Clinical Syphilis ..... 182
An Atlas of Human Anatomy ..... 183
A Doctor in Burma ..... 183
Notes on Books ..... 183

### OBITUARY

B. J. Brandson, M.D. ..... 195
John Murdoch, F.R.C.S.Ed. ..... 195
Ernest Ware, M.Ch., F.R.C.S. ..... 195
J. W. Hyslop, M.B., C.M. ..... 195
Henry Lloyd, M.D., D.P.H. ..... 195

**Epidemiology Section** ..... 197

### LEADING ARTICLES

**Localization in the Cerebrum and Cerebellum** ..... 184
**Epidemiology and Evacuation** ..... 185

### ANNOTATIONS

The Questionary ..... 185
Penicillin Production ..... 186
Research in Ophthalmology ..... 186
Malaria Control in N.E. India ..... 187
Miners' Diseases in the Past ..... 187

### REPORTS OF SOCIETIES

ROYAL ACADEMY OF MEDICINE IN IRELAND: Pneumoperitoneum ..... 189

### LETTERS AND ANSWERS

Blood Transfusion — Vaginal Pessary — Parasympathomimetic Drugs — Liquid Paraffin — Hypoproteinaemia — Twin Injections for Varicose Veins — Hay-fever—Skin Testing by Dust Extract— — Motility of Spermatozoa — Brittle Nails after Gastrectomy — Stubborn Asthma — Artificial Insemination — Unusual Ear Conditions—Clinical View of Shock — High Birth Weights — Trichomonas and Vaginal Discharge— Hospitality for Doctors' Children 198-200

### SUPPLEMENT

**British Institute of Public Opinion: White Paper and Questionary** ..... 25
**Proceedings of Council** ..... 29
MEDICAL WAR RELIEF FUND ..... 32
H.M. FORCES APPOINTMENTS ..... 32

### CORRESPONDENCE

Air Disinfection. C. C. TWORT, M.D., and others ..... 190
Fulminating Diphtheria. JAMES GRANT, M.D. ..... 190
The Surgeon and the Anaesthetic. HERBERT BROWN, M.D. ..... 191
Chloroform in India. K. E. MADAN, M.D. ..... 191
Meigs's Syndrome. W. F. T. HAULTAIN, F.R.C.S.Ed. ..... 192
Problem of the Small Bladder. H. P. WINSBURY-WHITE, F.R.C.S. ..... 192
Site for Intramuscular Injection. E. C. WYNNE-EDWARDS, F.R.C.S.Ed. ..... 192
Symptoms of Hiatus Hernia. V. C. MEDVEI, M.D. ..... 192
Chemotherapy in Otitis Media. H. M. STANLEY TURNER, M.D.; A. MACKENZIE ROSS, M.D. ..... 193
Septic Tonsils in the Soldier. E. S. B. HAMILTON, F.R.C.S.Ed. ..... 193
Episiotomy. G. S. N. DOW, M.B. ..... 193
Riboflavin and Allied Deficiencies. GRIFFITH EVANS, F.R.C.S. ..... 193
Epidemiology of Infective Hepatitis. C. H. WARNER, M.D. ..... 194
Self-medication and Patent Medicines. E. GRANGER, M.B. ..... 194
Varicella and Herpes Zoster. F. M. ROSE, M.B.; NORMAN FLOWER, B.M. 194
Adoption of Children. JAMES FENTON, M.D. ..... 194
Character in the Medical Student. H. E. VICKERS, M.B. ..... 194
Ophthalmologist and Optician. B. WILKINS, M.B. ..... 195

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 5 1944

# PENICILLIN: A SURVEY*

BY

**Sir H. W. FLOREY, M.B., Ph.D., F.R.S.**

*Professor of Pathology, University of Oxford*

The chemotherapeutic properties of penicillin were discovered in 1940, but before this there was a long history which for convenience can be divided into stages. (1) The discovery of naturally occurring antibacterial substances—or antibiotics, as they are now beginning to be called—and the early attempts to utilize them in medicine. (2) The discovery of the antibacterial substance penicillin by Alexander Fleming. (3) The discovery of its chemotherapeutic properties at Oxford. (4) The stage of development in which we are at present, which consists of three interrelated lines of research—namely, (i) exploration of methods for mass-producing penicillin by the growth of the mould *Penicillium notatum*; (ii) investigation of the chemical structure of penicillin with the hope that it may eventually be synthesized by chemical means; and (iii) the clinical exploitation of the known properties of penicillin.

## Stage 1

We have to go back to 1877 for the first observation of a naturally produced antibacterial substance. In that year Pasteur and Joubert described how when common air bacteria contaminated flasks of broth containing the bacillus of anthrax the growth of the anthrax bacillus was stopped. That phenomenon was probably the first observation that one organism may produce a chemical substance—or antibiotic—which is capable of stopping the growth of another, though Pasteur did not realize its true significance. In the succeeding years many examples were discovered, of which the most interesting was *Bacillus pyocyaneus*. From the medium on which this organism had grown Emmerich and Loew extracted a substance which they called pyocyanase. This was found to be capable of stopping the growth of certain organisms causing disease, notably anthrax and diphtheria. They applied it to the lesions of the skin caused by anthrax with, they claimed, some benefit. Although this product was on sale in Germany as recently as the 1930's its use in medicine never became widespread.

## Stage 2

In 1928 Fleming was studying the staphylococcus. One day he examined and then put aside on his bench a plate on which colonies of the staphylococcus were growing. Several days later there was a colony of mould growing on one side. Fleming noticed that in the neighbourhood of the mould the colonies of staphylococci were disappearing. He recognized this as a phenomenon of interest, and subcultured the mould, which was later identified as *Penicillium notatum*. When grown on nutrient broth it was found to produce some substance which passed into the liquid.* By experiments in test-tubes Fleming showed that the liquid had the property of stopping the growth of many bacteria. Fleming called the active liquid penicillin. He carried out experiments on the effect of his broth on numerous organisms in test-tubes and showed that many which can cause disease in man were affected, although some disease-producing organisms were quite insensitive. He also injected some of the broth containing penicillin into rabbits, and found that it was no more toxic than ordinary broth. He found, too, that the broth did not harm the white blood cells. Fleming, who had been working on antiseptics, recognized that penicillin had some very desirable properties as an antiseptic, and proposed that it might be useful for local application to infected surfaces. He did, in fact, so apply it in a few cases, with results indicating, as he said, that "it certainly appeared to be superior to dressings containing potent chemicals." About this time an attempt was made by Clutterbuck, Lovell, and Raistrick to extract the penicillin. They succeeded in growing the mould on a purely synthetic medium and found that the active substance could be extracted into ether when the watery medium containing penicillin was acidified. However, when they tried to concentrate the penicillin by evaporating the ether most of the activity was lost, and they concluded that penicillin was "extremely labile."

We may briefly summarize the position at the end of this phase by saying that Fleming had discovered the existence of an antibiotic produced by *Penicillium notatum*. Some test-tube investigations had been made of the antibacterial power of the crude broth and, as a result, it had been suggested that it might be useful as an antiseptic locally applied to infected lesions. But as the result of both Fleming's and Clutterbuck, Lovell, and Raistrick's work the conclusion had been reached that penicillin was an unstable substance and therefore unlikely to have any practical value in medicine.

## Stage 3

Stage 3 deals with the work done at Oxford. My own interest in the phenomena of bacterial inhibition began in the 1920's. Since 1929, at first alone and later with collaborators, work had been in progress, but it was not till 1938 that Dr. Chain, a biochemist, and I prepared a plan for the systematic study of some of the naturally produced antibacterial substances. After much discussion the choice was narrowed down to three—*Bacillus pyocyaneus*, *Penicillium notatum*, and the subtilis-mesentericus group of bacteria. Eventually work was undertaken on the first two. Miss Schoental obtained three antibacterial products from *Bacillus pyocyaneus*, which all proved to be very toxic, but fortunately the results with penicillin turned out rather differently.

Both Fleming and Clutterbuck, Lovell, and Raistrick had noticed that under certain conditions the crude broth might retain its activity for at least several weeks. This indicated that in appropriate conditions the substance might not be so unstable as had been pictured. To work on the metabolic products of moulds from biological as well as chemical aspects needs a team of specialized workers, so that the various fields of investigation may be covered, and it was most fortunate that such a team was available in Oxford at that time. I should like to stress that this work could not have been carried through had it not been for the unremitting labours of the following people: Dr. Chain, Dr. Abraham, Prof. Gardner, Dr. Heatley, Dr. Jennings, Dr. Sanders, Dr. Fletcher, and Lady Florey. Nor

* Abridgment of the Peter Le Neve Foster Lecture delivered before the Royal Society of Arts on June 7, 1944.

could we have got far without the work of our technical assistants, Mr. Glister and his "penicillin girls," Mr. Kent, and, for the chemical work, Mr. Callow and Mr. Burtt.

The body of work done by this team in the next two years produced a single end-result—penicillin as a proved chemotherapeutic drug. The steps cannot be set out chronologically because different aspects of the work were in progress simultaneously, and the accent was first on one thing and then on another until a fairly complete picture was built up. The first step in all work of this type is to grow the mould on a medium into which it will produce the active substance. Here we were able, in the first place, to use the information which had been obtained by Fleming and by Clutterbuck, Lovell, and Raistrick, and we began by growing the mould on the synthetic medium proposed by the latter workers.

In studying an antibiotic its fundamental property of inhibiting bacteria can be made use of as a test method, and we owe to Dr. Heatley the elaboration of a test which has proved invaluable for work not only on penicillin but on many other antibiotics as well. By means of his method it was possible to follow the various fractionating processes. The crucial chemical observation was the demonstration that not only did penicillin, when made acid, pass from a watery into an organic solvent such as ether or amyl acetate, but that it could be recovered from the organic solvent when shaken with water and an appropriate amount of alkali. By repetitions of this process purification and concentration were effected and the first stable products containing penicillin produced.

### Chemical Properties of Penicillin

The principal chemical properties of penicillin are these: (1) An acid, unstable in the acid form but stable as salts between *p*H 5 and *p*H 7. (2) Ba, Ca, and Na salts highly soluble. (3) Destroyed by acids and alkalis and by heating. (4) Inactivated by oxidizing agents, heavy metals, primary alcohols, and ketonic reagents. (5) Inactivated by enzymes produced by some common bacteria.

This last is a very important observation, because it explains why large-scale production has proved to be more than usually difficult. The ubiquitous air bacteria may produce ferments which destroy the penicillin as fast as the mould makes it, so that although the mould may appear to grow well no penicillin is produced. As a consequence, all penicillin has to be manufactured with the exclusion of all air bacteria, and to do this on a large scale is a very difficult technical feat.

The production of a partly purified extract made possible the biological investigations which formed the next stage. It was found that the extract, even when highly diluted, would stop the growth of many organisms causing disease.

#### Bacteria Sensitive to Penicillin

Gram-positive.—*Streptococcus pyogenes, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus viridans, Bacillus anthracis, Corynebacterium diphtheriae, Actinomyces bovis, Clostridium tetani, Cl. welchii, Cl. septique, Cl. oedematiens.*

Gram-negative.—*Neisseria gonorrhoeae, N. meningitidis.*

#### Bacteria not Sensitive to Penicillin

Relatively insensitive.—Gram-negative: *Salmonella typhi, S. gaertneri, Vibrio El Tor.*

Almost or completely insensitive.—Gram-positive: *Mycobacterium tuberculosis.* Gram-negative: *Pasteurella pestis, Vibrio cholerae, Bacterium coli, Pseudomonas pyocyanea, Proteus, Brucella abortus, Br. melitensis, Bacillus of Friedländer.*

This list is substantially the same as Fleming found with his crude broth containing penicillin, with the important addition among the sensitive organisms of the bacilli of gas gangrene and, unhappily, among the insensitive of the tubercle bacillus. Only those diseases caused by sensitive bacteria are susceptible of cure by penicillin. It was shown that penicillin, except possibly in very strong solution, does not kill the bacteria, but is a bacteriostatic. The penicillin preparations which we had at that time were bacteriostatic for sensitive bacteria at the dilution of 1 in 1 million, but we now know that these were very impure products. Pure penicillin will stop the growth of some kinds of bacteria at the astonishing dilution of 1 in 50 million or more.

It was further shown that the activity of the substance was maintained with scarcely any diminution in serum, in pus, and in the presence of autolysed body tissues. During the process of autolysis many breakdown products are formed, but none of them interfere with the action of the penicillin. These properties differentiate penicillin very sharply from the sulphonamide group of drugs, which are rendered largely ineffective by pus or tissue breakdown products. Another important finding was that penicillin would act almost equally well when large numbers of bacteria were present as when there were few; in either case it would inhibit the growth of the whole lot. This again is in sharp contrast to the sulphonamides, which are rendered less effective if many bacteria are present.

The fact that penicillin is a very powerful antibacterial agent would not by itself differentiate it from a number of other mould products or from some of the familiar chemical antiseptics. But whereas nearly all such substances are quite toxic to body tissues, even concentrated extracts of penicillin had practically no poisonous action on animals. It was further shown that individual body cells, such as the white cells of the blood, were unaffected by concentrations many hundreds of times greater than those necessary to stop the growth of sensitive organisms.

When administered to an infected animal or man in sufficient quantity penicillin stops the growth of the germs, thus giving the white blood cells in particular, and possibly other defence mechanisms, the opportunity effectively to attack and destroy them. It was found, too, that tissue cultures would survive and grow in concentrations very much greater than those necessary to produce bacteriostasis. In animals the active material was rapidly excreted by the kidneys into the urine, and, to a lesser extent, by the liver into the bile. It was readily absorbed after injection under the skin or into the muscles or into the small intestine, but it could not be given by mouth because of the hydrochloric acid in the stomach, which destroys penicillin very rapidly. Neither could it be given by the large bowel because the bacteria there destroy it.

The position at which we had now arrived was that we had in our hands a substance which combined very low toxicity to animals with a very powerful action against disease-producing bacteria. We knew a good deal about its fundamental behaviour in the animal body. The most important step had now been reached—we had still to learn whether it would cure disease in animals and man.

It is worth while to digress for a moment in order to take up the question of antiseptics, so that the real significance of the experiments about to be described may be understood. Everyone is familiar with antiseptics such as mercuric chloride, acriflavine, dettol, lysol, etc. All these are capable, under appropriate conditions, of killing bacteria—mark the word "killing"—but cannot be used for injecting into the animal body because they have a damaging effect on animal cells as well as on bacteria. All the antiseptics in common use destroy protoplasm quite quickly, and this applies equally to the protoplasm of the bacterium and of the animal. As might be expected, although antiseptics can be used for sterilizing instruments and similar purposes, little success has attended their use in dealing with infected wounds, still less their injection into the body. A chemotherapeutic agent differs from antiseptics in that it selectively attacks the organisms causing the disease without at the same time doing any serious injury in the body. For this reason it can be given internally or by injection. There are several examples of such chemotherapeutic substances. The one which has been known the longest, and is perhaps the most familiar, is quinine, used to combat malaria. Quinine is swallowed by mouth, passes into the blood stream, and exerts its beneficent action in killing the malaria parasite while being carried round to all parts of the body. Another example is salvarsan, the discovery of Ehrlich, produced after many years' work. It is an arsenic compound which has a very profound effect on the spirochaete of syphilis without being too toxic to be borne by the person suffering from the disease. Other substances were discovered which were effective against various tropical diseases, but only one class of substance, the sulphonamides, had been found of any use in common diseases

such as sepsis. Their use was, for various reasons—some of which have been mentioned earlier—somewhat limited. These are all true chemotherapeutic agents, not antiseptics.

The following experiments demonstrated that penicillin belongs to the class of true chemotherapeutic agents. So far as the use of penicillin in medicine is concerned this was the crucial discovery. Such experiments are carried out in the following way. Mice are injected with bacteria such as streptococci and staphylococci so that they will certainly die from the infection within one or at most two days. To show that a substance suspected of having chemotherapeutic properties is active it is necessary to secure survival of a substantial number of mice which would otherwise certainly die. In the case of penicillin this was accomplished by injecting some penicillin under the skins of the infected animals every three hours for several days. The drug was absorbed from beneath the skin into the blood stream, which carried it to the place where the infecting bacteria had previously been placed. Knowing that penicillin was a soluble substance quickly distributed round the body, that it was not toxic to animal tissues, and that it was just as active in the presence of body tissues as in a test-tube, we were justified in hoping that it would stop the bacteria growing as effectively in the body as it did outside. And this proved to be the case. The groups of treated mice survived almost without exception, while the untreated mice all died. These first experiments indicated without any doubt that penicillin belonged to that rare class of drugs which can be used as chemotherapeutic agents.

From this demonstration it appeared that penicillin was likely to have very great potentialities in the field of human medicine. Penicillin at that time was extremely difficult to produce in substantial quantities, so that some time passed before we were able to show its powers on man. We again have to thank Dr. Heatley and his assistants for unremitting work in producing in the laboratory enough penicillin for the first injections in man. Even after months of work we could treat only six cases of severe infection, but the results were most promising.

The first human patients were treated in the winter and spring of 1940–1, at the time of the worst bombing of England. It seemed improbable that much headway could be made in getting large-scale production started in this country. In these circumstances Dr. Heatley and I went to America, which was not then at war, to ask them whether they could put some of their great resources into the production of penicillin, so that more extensive clinical trials could be carried out. We were extremely fortunate in coming into contact with Dr. Coghill, Director of the Fermentation Division of the Department of Agriculture's excellent research laboratory at Peoria, in Illinois. The work which he and his colleagues have done on the selection of high-yielding strains of *Penicillium notatum*, and on the modification of culture media, has greatly increased the yield which can be obtained from the mould, and has played an important part in the large-scale production of penicillin.

While this work was being initiated in America, enough material was made in Oxford and by Imperial Chemical Industries to enable some eighteen patients with severe infections, most of them caused by the staphylococcus, to be treated. These results were again of such great promise that any effort to produce the drug on a really large scale was clearly worth while. This was more so since certain of the bacteria susceptible to penicillin cause some of the most common and universal infections, including those of war wounds.

### Stage 4

From that time the work branched in three directions. First, it was clear that it would be very desirable to make the substance synthetically by chemical procedures without the intervention of the mould. Work is now proceeding along these lines in Oxford, where Dr. Chain and Dr. Abraham are collaborating with Sir Robert Robinson and his colleagues, and elsewhere, both in this country and in America, hundreds of chemists are engaged on this important problem. Progress in this direction cannot be reported as it is now in the secret category, but the fact has already been published that pure penicillin has been obtained. This was done in America and in Oxford at about the same time. Every resource has been mobilized to deal with this chemical question, but whether success will attend the effort to produce penicillin by synthesis it is impossible to forecast.

The second, and more immediately practicable line, has been to increase the manufacture by means of the mould to a really large scale. This has involved a large number of intricate technical problems, which have been tackled along different lines by the various commercial firms, both in this country and in America. As a result of their efforts penicillin can now be issued by the kilogramme, although, of course, the supplies still fall lamentably short of the demand.

The third line has been to explore further the use of penicillin as a curative agent. There are two possible ways of using penicillin. First, it can be injected into the muscles or veins so that it is carried around in the circulation to the parts which are being attacked by the infecting bacteria. This method is obligatory in the more serious and widespread diseases such as pneumonia, diseases of the bones, and septicaemia, where the diseased tissues cannot be reached by any other means. Although in many cases this is a very effective method, it has the disadvantage of requiring relatively large amounts of penicillin, since the drug is rapidly excreted by the kidneys. Secondly, penicillin may be used as a local application to the affected part. This can be undertaken only if every portion of the infected tissues can be reached by the penicillin, and a good deal of the success of local application depends upon surgical ingenuity in ensuring that the penicillin, which is rapidly absorbed from a wound, is kept in contact with all the infected tissues long enough to exert its action. At the present time a great deal of thought and study is being given to the problem of war wounds and how best to utilize penicillin, both locally and generally, for their treatment.

The increasing supplies of penicillin now available permit of extensive explorations of its use in many diseases. Perhaps the most striking recent addition to knowledge is that of the Americans, who have discovered that penicillin is apparently effective in treating syphilis. Another excellent development since larger supplies have become available is that penicillin can now be given as a preventive instead of as a last resort. In battle casualties especially, the effort is being made to prevent serious sepsis from developing by giving penicillin at a very early stage.

## TREATMENT OF ACUTE EMPYEMA WITH PENICILLIN

BY

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AND

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*Physician in Charge of Inoculation Department, the London Hospital; Pathologist, E.M.S.*

Treatment of acute empyema has both immediate and ultimate aims—the former to overcome the toxaemia by sterilizing or draining the cavity, the latter to restore the function of the lung and chest wall. This investigation is intended to show how far penicillin can assist in the realization of these aims when it is used in the simplest possible way—repeated emptying of the cavity by aspiration, followed by injection of the drug into it. Penicillin was dissolved in water to give a concentration of 1,000 units per c.cm., and the dosage was adjusted to the size of the cavity. The sensitivity of the infecting organism having been established, the initial injection varied between 10,000 and 40,000 units, 20,000 being usual. As treatment proceeded 10,000 or 5,000 units often sufficed. Tests for the presence of the drug in the pus withdrawn provide essential guidance in this respect. In the cases in which multiple loculi were present each cavity was treated on the same lines. It

was soon found that treatment on alternate days was adequate in the ordinary case, but the presence of a broncho-pleural fistula, associated with the rapid disappearance of the drug from the pleural cavity, may render more frequent injections necessary. Our supply did not permit us to supplement local with systemic therapy, which may be desirable in some, if not all, cases.

So far, 18 cases (Table I) have been treated. They show the variations to be expected in such a series in regard to age, sex, site of lesion, loculation, infecting organism, underlying lung condition, and broncho-pleural fistula, any of which may be of the greatest importance when considering the individual case. But as treatment proceeds they also tend to show certain common features, such as have been described by workers both in this country and in the United States. To illustrate this, one case (No. 4) is described below in detail, the course of the others being shown in the table and their special features discussed when necessary.

FIG. 1.—Case 2; woman aged 60. Right empyema; pneumococcus Type 28. (Oct. 5, 1943.)

FIG. 3.—Case 4; man aged 53. Right empyema after emptying cavity by aspiration. Haemolytic streptococcus. (Jan. 8, 1944.)

### Case 4

The patient, a male omnibus driver aged 53, had a right-sided empyema, the largest aspiration from which was 3 pints of pus. The infecting organism was a haemolytic streptococcus. He developed a cough 25 days before admission, followed in 3 days by pain in the right side of the chest. One week later he was admitted to Oldchurch Hospital, under Dr. W. J. Stokes, in a toxic distressed condition with signs of a large right pleural effusion, which on aspiration showed the presence of pus and haemolytic streptococci. He was treated by aspiration and 40 g. of sulphapyridine. He was still in a toxic condition when admitted to Claybury Emergency Hospital on Dec. 9, 1943. There was stony dullness, with absence of breath sounds, over the right side of the chest. This was aspirated, and thin pus was obtained from which haemolytic streptococci were grown.

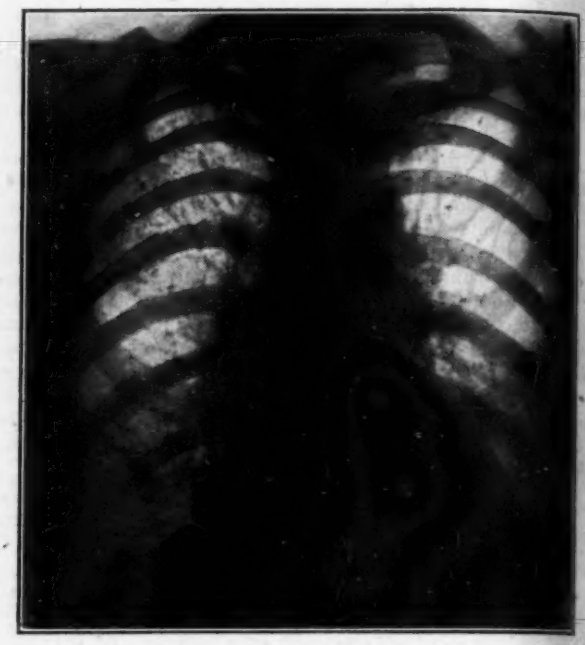

FIG. 2.—Case 2 at May 25, 1944.

FIG. 4.—Case 4 at May 10, 1944.

Aspiration and injection of penicillin began on the day of admission, and were continued on alternate days until Jan. 5, 40,000 units being given on the first day and thereafter 20,000 or 10,000 units. The pus withdrawn remained sterile on culture after the first injection, and steadily thickened until, after 14 days' treatment, the deposit on standing took up the whole volume of fluid. During this period the appearance of the streptococci as stained by Gram's method gradually changed until by the 10th day of treatment all were atypical, showing as minute Gram-positive dots, often in clusters. Pus continued to collect at intervals, causing slight fever, but otherwise appearing to be of the cold abscess type; and the minute cocci, sterile on culture, persisted until Feb. 24. The last aspiration, however—on April 4—withdrew 40 c.cm. of clear fluid containing lymphocytes. During this prolonged period radiographs

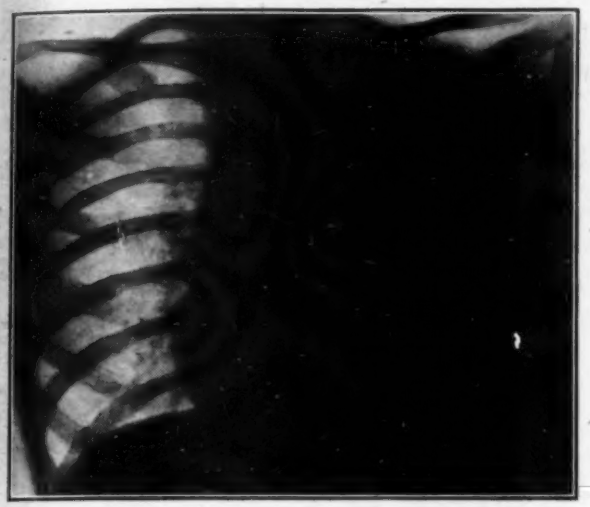

FIG. 5.—Case 8; boy aged 10. Left empyema; pneumococcus Type 1. (Jan. 23, 1944.)

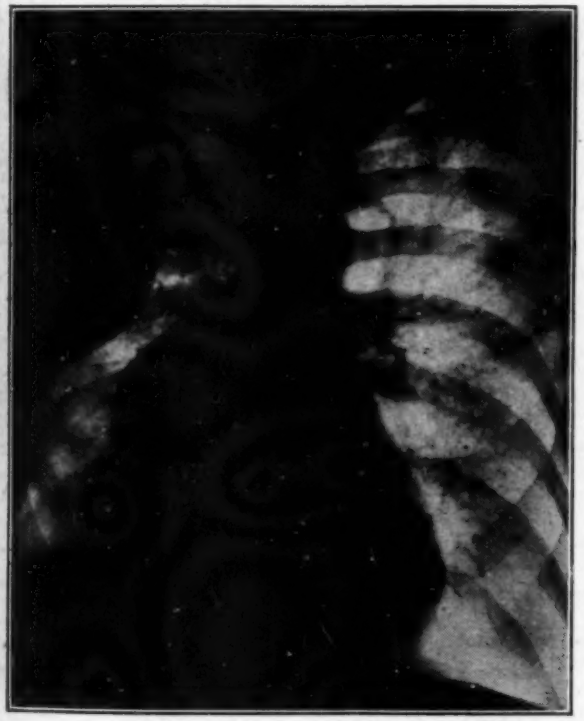

FIG. 7.—Case 10; man aged 49. Right empyema showing postero-lateral and antero-medial pockets; pneumococcus Type 2. (March 20, 1944.)

taken after aspiration showed a progressively lessening cavity with thickened walls (Figs. 3 and 4). At the time of writing the patient is well and back at work, but the chest wall is sunken and immobile over the affected area; however, serial radiographs show that the lung is still re-expanding.

This brief account will serve to suggest certain problems that arise during the treatment described. The cavity was sterilized, but it was difficult to say when this was finally accomplished. The prolonged pus formation after sterilization of the cavity, maintaining pulmonary collapse, and increasing pleural thickening were, however, a disappointing feature.

### The Remaining Cases

Table I gives details of all the cases under discussion. They include four cases of infection with haemolytic streptococci, three

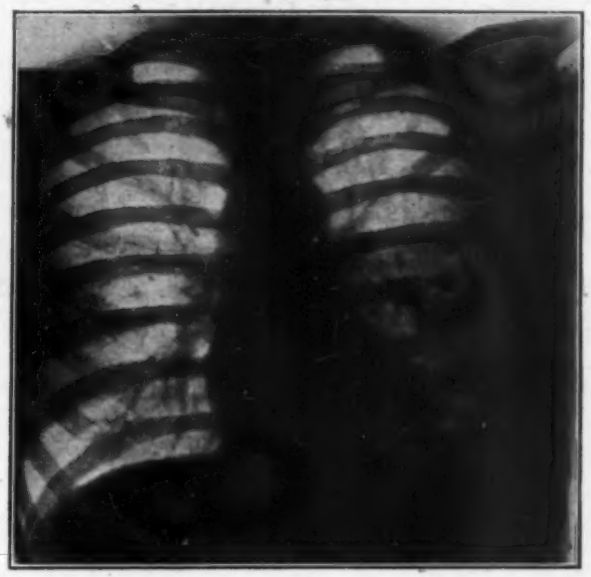

FIG. 6.—Case 8 at May 5, 1944.

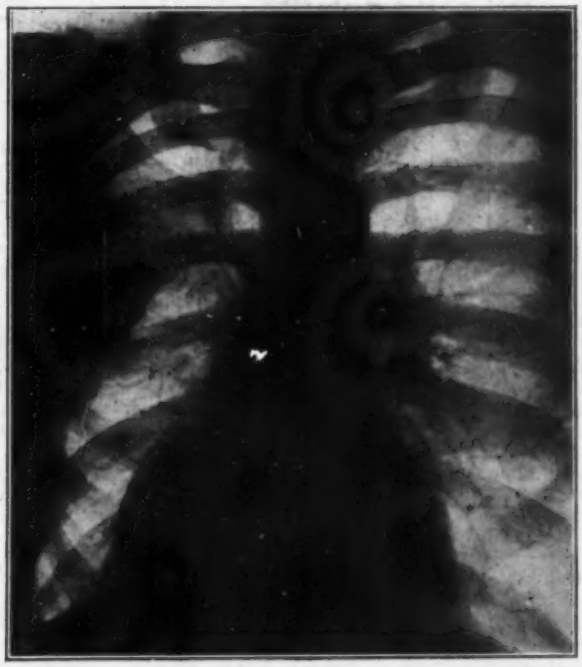

FIG. 8.—Case 10 at May 26, 1944.

with non-haemolytic streptococci, one with a micro-aerophilic streptococcus, and one with an anaerobic streptococcus. There were seven cases of pneumococcal infection and one case from which a haemolytic streptococcus was first isolated, to be followed later by a pneumococcus.

In every case, except No. 17, in which there was a broncho-pleural fistula, the cavity was sterilized with a dosage of penicillin ranging from 40,000 to 200,000 units, but it is not easy to determine the period of injections adequate to ensure permanent sterility. Cultures of the pus are often found to be sterile after one injection

TABLE I.—*Details of 18 Cases*

| No. | Sex | Age | Side | Complicating Disease | Organism in Empyema | Total Units of Penicillin | Weeks Febrile | No. of Aspirations | Most Pus Removed at Single Aspiration | Day of Final Aspiration | Present Condition |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 55 | Right | Perforated appendix | Non-haemolytic streptococcus | 40,000 | 2 | 4 | 18 oz. | 23 | After reconstruction of abdominal wall: Well. No cough; little pleural thickening. At work |
| 2 | F | 60 | ,, | | Pneumococcus Type 28 | 80,000 | 8 | 11 | 4 oz. | 2 | Well. Taking normal exercise. (Figs. 1 and 2) |
| 3 | F | 71 | ,, | | ,, Type 8 | 40,000 | 4 | 7 | 8½ oz. | 21 | Well. No pleural thickening. Taking normal exercise |
| 4 | M | 53 | ,, | | Haemolytic streptococcus | 270,000 | 9 | 21 | 60 oz. | 85 | Well and at work. Considerable pleural thickening. (Figs. 3 and 4) |
| 5 | F | 19 | Left | | ,, ,, | 155,000 | 4 | 10 | 20 oz. | 18 | Well and at work. Pleural thickening |
| 6 | F | 28 | Right | Tuberculosis R. zones 1 & 2; right artificial pneumothorax; division of adhesions. Haemorrhage; secondarily infected | Anaerobic streptococcus | 155,000 | 12 | 12 | 13 oz. | 28 | Haemoglobin 70%. Blood transfusion. Now afebrile. Small effusion, which is sterile. Sanatorium |
| 7 | M | 52 | ,, | | Pneumococcus Type 1 | 80,000 | 1 | 8 | 11½ oz. | 20 | Well. Some pleural thickening |
| 8 | M | 10 | Left | | ,, ,, | 135,000 | 5 | 13 | 13 oz. | 49 | Well; back at school. No scoliosis; no thickening July. (Figs. 5 and 6) |
| 9 | F | 31 | Right | Very severe rheumatoid arthritis | Haemolytic streptococcus | 100,000 | 4 | 10 | 5 oz. | 32 | Well. Considerable pleural thickening |
| 10 | M | 49 | ,, | | Pneumococcus Type 2 | 200,000 | 5 | 16 | 12 oz. | 46 | Well and at work. Developed antero-medial and postero-lateral pockets with marked pleural thickening in each. (Figs. 7 and 8) |
| 11 | M | 41 | Left | | ,, Type 1 | 95,000 | 2 | 9 | 24 oz. | 20 | Became sterile after 55,000 units, but pneumococci reappeared. Little pleural thickening. Back at work |
| 12 | M | 2 | ,, | Streptococcal pemphigus; streptococcal bursitis over left elbow | Haemolytic streptococcus; secondarily, pneumococcus Type 19 | 95,000 | 8 | 5 | 18 oz. | — | Improved from a moribund condition, but developed broncho-pleural fistula, necessitating rib-resection and drainage, 22/4/44. Condition again deteriorated; died 20/5/44. No necropsy |
| 13 | M | 59 | Right | | Pneumococcus Type 24 | 45,000 | 2 | 5 | 15 oz. | 17 | Became sterile after 25,000 units, but with appearance of broncho-pleural fistula became reinfected. No pleural thickening. Back at work |
| 14 | M | 21 | ,, | Traumatic haemothorax from bullet wound | Sterile | 30,000 | 1 | 6 | 12 oz. | 14 | Well. Returned to unit |
| 15 | M | 52 | Left | | Non-haemolytic streptococcus | 60,000 | 1 | 4 | 23 oz. | 37 | Well. Some pleural thickening |
| 16 | F | 32 | Right | Mitral stenosis; pulmonary infarct | ,, ,, | 90,000 | 1 | 7 | 8 oz. | 22 | Greatly improved |
| 17 | M | 52 | Left | | Micro-aerophilic streptococcus | 230,000 | 7 | 8 | 44 oz. | — | Condition never satisfactory, as penicillin rapidly disappeared from pleural cavity probably owing to broncho-pleural fistula. 6/5/44: Rib-resection and drainage; condition continued to deteriorate. 23/5/44: Died. Necropsy: Empyema; pulmonary and subdiaphragmatic abscesses; fibrosis of lung and bronchopneumonia; pericarditis |
| 18 | F | 70 | Right | Left radical mastoid operation | Haemolytic streptococcus | 60,000 | 1 | 4 | 23 oz. | 21 | Greatly improved. Some pleural thickening |

of penicillin, but withdrawal of the drug at this stage would invite recurrence. Table II indicates the sequence of events in 12 uncomplicated cases—7 streptococcal and 5 pneumococcal. The table shows the period of continuous administration of penicillin in each case, the day on which the pus gave a sterile culture, and that on which all the cocci in the pus were of the abnormal small type described in the account of Case 4. It will be seen that with pneumococci the change in appearance coincides with, or follows closely, the first sterile culture, but in the case of streptococci there is a longer interval. But even with the latter organism it was found to be unsafe to use this test as an indication for stopping the injections, as the recurrence of infection in Cases 15 and 16 shows. It is noticeable that in five cases in which active infection recurred it was between the 16th and 19th days, but this may well have been due to chance.

Cases 7 and 11 were instances of pneumococcal infection giving thin pus in which the agglutination of the cocci showed the presence of antibody. These patients had few toxic symptoms. In Case 8 the cocci were present in enormous numbers, unagglutinated and within intact capsules, and the patient was desperately ill. The fact that there was a recurrence in Case 11 suggests that the presence of antibody, beneficial in other respects, may not affect the period necessary for permanent sterilization of the cavity.

Case 10 shows the loculation which often occurs in pneumococcal cases (Figs. 7 and 8). There was an antero-medial pocket, the pus from which became sterile on the 14th day, whereas that from the postero-lateral pocket did not become sterile until the 20th day.

Of special interest was Case 6, that of a young woman aged 28 who developed a tuberculous pyopneumothorax after haemorrhage during the division of adhesions. This became secondarily infected with an anaerobic streptococcus. The organism was killed after administration of 155,000 units of penicillin, and the patient became afebrile and was able to go to a sanatorium.

TABLE II.—*12 Uncomplicated Cases*

| Case | Bacteria | Continuous Penicillin Treatment | Sterile | Cocci all Abnormally Small | Recurrence | Antibody |
|---|---|---|---|---|---|---|
| 4 | Haem. strep. .. | 39 days | 2 days | 10 days | — | |
| 5 | ,, ,, .. | 10 ,, | 2 ,, | 8 ,, | 16th day | |
| 7 | Pneumococcus | 9 ,, | 2 ,, | 2 ,, | — | Present |
| 3 | ,, | 5 ,, | 1 ,, | 1 ,, | — | |
| 2 | ,, | 8 ,, | 3 ,, | 3 ,, | 17th day | |
| 6 | Anaerobic strep. | 28 ,, | 4 ,, | 10 ,, | — | |
| 9 | Haem. strep. .. | 22 ,, | 5 ,, | 22 ,, | — | |
| 8 | Pneumococcus | 12 ,, | 2 ,, | 4 ,, | — | Absent |
| 11 | ,, | 9 ,, | 2 ,, | 5 ,, | 16th day | Present |
| 15 | Non-haem. strep. | 9 ,, | 9 ,, | 9 ,, | 19th day | |
| 16 | ,, ,, | 6 ,, | 2 ,, | 4 ,, | 18th day | |
| 18 | Haem. strep. .. | 14 ,, | 2 ,, | 12 ,, | — | |

Case 14 was that of an American military policeman who was shot through the chest and developed a traumatic haemothorax. After as much blood as possible was aspirated he was given thor

injections of 10,000 units of penicillin on successive days. He made an uneventful recovery.

### Discussion

The above cases show that, provided the infecting organism is susceptible, an empyema cavity can be sterilized by repeated aspiration of the pus and injection of penicillin, and that the toxic condition is thereby relieved. This confirms the findings of Keefer and his colleagues (1943), Bennett and Parkes (1944), Christie and Garrod (1944), Dawson and Hobby (1944), Herrell (1944), and Bloomfield and his colleagues (1944).

It is too early to assess the final results of the treatment, since further improvement is expected in some cases, while others may yet develop symptoms arising from pulmonary fibrosis. But it already seems probable that the simple methods employed, though sometimes satisfactory, especially in elderly patients such as Cases 2 and 3, are at other times insufficient. The persistence of a purulent effusion is undesirable if pleural thickening and fibrosis of the lung are to be minimized. In our series the period required for final sterilization of the cavity was unpredictable, since Cases 2, 5, 11, and 15 showed recurrence after 8 to 10 days of continuous treatment, whereas Case 3 remained sterile after only 5 days' treatment. Recurrence was found to be easily controlled by a second course of penicillin.

After sterilization there was the tendency for sterile pus to be formed in which minute Gram-positive cocci persisted; and it seems possible that these organisms, although dead, may remain pyogenic. The source of these organisms and of normal cocci in cases of recurrence is probably to be found in the masses of fibrinous exudate lining the walls of the cavity, the removal of which might be expected to hasten sterilization and limit the formation of pus. For this reason Pilcher (1944) advocates washing out the cavity with sterile saline through a rubber catheter until the returned fluid is clear, before injecting penicillin, whereas Tubbs recommends rib-resection and removal of the fibrinous masses lining the cavity as soon as the infection is under control and the patient fit for the operation. There is little hope of avoiding a thickened pleura and rigid chest wall without removal of the fibrinous masses, and it seems reasonable to believe that this can be achieved only after a rib-resection. The removal of this fibrinous material will also help to avoid recurrence of the empyema in such cases at a later date. The presence of grave toxaemia indicates a lack of specific immunity and the probability of underlying pneumonia. General treatment is clearly desirable, but sulphonamides, except in the case of a resistant organism, might usually be found as satisfactory as penicillin. The use of type-specific antipneumococcal serum, if available, might also hasten the restoration of the lung in these cases. Breathing exercises will encourage re-expansion of the lung in the convalescent stage.

In secondarily infected tuberculous pyopneumothorax the ability to remove the invading organism will constitute a great advance and will entirely alter the prognosis of this serious complication of pulmonary tuberculosis.

Tudor Edwards (1943) has shown that the incidence of infection in traumatic haemothorax caused by penetrating wounds is 21.9%, and by non-penetrating ones it is 11.3%. Our one case was caused by a penetrating wound, and infection did not occur. It seems justifiable to hope that penicillin will play a decisive part in preventing infection in these cases.

### Summary

A report is given on 17 cases of empyema treated with penicillin. In 10 the invading organism was the streptococcus and in 7 the pneumococcus.

Penicillin will normally sterilize the pleural cavity, provided that the infecting organism is penicillin-sensitive. Aspiration alone, however, often leaves a thickened pleura and a rigid chest wall, with the consequent disabilities of reduced vital capacity, fibrosis, and risk of recurrent pulmonary infection. Rib-resection is frequently necessary to remove the masses of fibrin which collect in the cavity and thus avoid these complications.

One case was a secondarily infected tuberculous pyopneumothorax in which the invading streptococcus was killed by penicillin.

One traumatic haemothorax with a penetrating wound was successfully treated with penicillin to prevent infection.

We are indebted to Prof. R. V. Christie and to the Committee on Clinical Trials of Penicillin of the Medical Research Council for the supplies of penicillin.

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## PENICILLIN IN OPHTHALMOLOGY

BY

**J. G. MILNER, F.R.C.S.**

*Squad. Ldr., R.A.F.V.R.*

This report comprises a series of cases investigated by different observers: Series I, by Squad. Ldr. Sampson, R.A.F.V.R.; Series II, by Squad. Ldr. Burr, R.A.F.V.R. (and others); Series III, by Squad. Ldr. Palin, R.A.F.V.R. (and others); Series IV, by Squad. Ldr. Milner, R.A.F.V.R. In compiling the report I have tabulated the several results separately, with the comments of the various observers. Finally a brief summary of the results as a whole is given. A comprehensive analysis was made possible by ensuring that all observers used the same source of supply of penicillin. Dosage and method of treatment were the same at the different hospitals. The cases were treated between mid-December, 1943, and the end of March, 1944.

### Preliminary

1. *Strength and Dosage.*—The drug was used (1) as drops, 500 Oxford units per c.cm.; (2) as ointment, 100 Oxford units per gramme—made up in lanette wax and vaseline. Dosage was uniform so far as was possible. Three drops were instilled into the conjunctival sac three times a day, making a daily dosage of 250 units. Ointment was used in blepharitis and acute conjunctivitis, the daily dosage being approximately 30 units. The only other treatment employed was a preliminary irrigation with normal saline; 1% atropine drops were also used where indicated.

2. *Local Reaction.*—About 50% of the patients complained of smarting after the application of drops; this soon dispersed. The majority of those having ointment stated that it was more irritant than drops, the effect lasting about 10 minutes.

3. *Activity of Penicillin.*—Some experiments were carried out for me by Squad. Ldr. Leslie, R.A.F.V.R., to determine how long penicillin remained potent in the conjunctival sac. Two assessments were made on the same patient, using the same eye, an interval of several days elapsing between the experiments.

A. Two drops of penicillin (500 units per c.cm.) were instilled into the conjunctival sac at 9 a.m. Specimens of conjunctival secretion were taken at hourly intervals and estimated for their inhibitory effect against constant amounts of a known dilution of an 18-hour broth culture of a penicillin-sensitive staphylococcus. The following technique was used: (i) Specially prepared pipettes calibrated to deliver 10-c.mm. drops. (ii) 1 drop (10 c.mm.) of conjunctival secretion was added to 1 drop (10 c.mm.) of sterile human serum and thoroughly mixed with one loopful (approximately 0.5 c.mm.) of a 1/1000 dilution of an 18-hour broth culture of a standard staphylococcus provided by the Central Laboratory at Halton (Oxford strain 1). The admixture was carried out on a sterile slide and the mixture covered with a sterile cover-slip and sealed with molten paraffin wax. The "cells" thus prepared were incubated at 37° C. for 24 hours. (iii) The control cell was set up. This consisted of two 10-c.mm. drops of sterile human serum plus a loopful of the staphylococcus suspension treated in the same way as the other cells. (iv) A second control, consisting of two 10-c.mm. drops of normal conjunctival secretion, was used, to which was added a loopful of staphylococcus suspension treated as above. This produced a good growth of colonies.

*Result.*—The growth of staphylococci was completely inhibited in the first 4 cells. There was no inhibition in the 5th-hour specimen as compared with the control, which yielded a good growth of discrete colonies.

B. This experiment was conducted in exactly the same way as A, with the following modifications: (i) Penicillin ointment (100 units

per gramme) was used instead of drops. (ii) The same penicillin-sensitive staphylococcus was employed as in A, but a 1/500 dilution of an 18-hour broth culture was substituted for the 1/1000 dilution used in experiment A.

*Result.*—The growth of the staphylococcus was completely inhibited in the first 5 cells—i.e., 5 hours. The 6th-hour cell showed partial inhibition of a fairly high degree (there were 3 colonies in this cell, as compared with 27 in the control cell). A standard loopful of the staphylococcus dilution subcultured on a blood-agar plate and incubated at 37° C. for 24 hours yielded 33 colonies.

From these experiments it is clear that penicillin drops are potent for 4 hours and ointment for 6 hours. Frequency of treatment can be regulated accordingly.

4. *Type of Case Treated.*—Blepharitis, styes, dacryocystitis, conjunctivitis, infective corneal ulceration, and infective chalazion are obvious choices. Besides these, penicillin was tried in episcleritis, trachoma, disciform keratitis, dendritic and marginal ulcer, and mild conjunctival hyperaemia (such as is associated with allergy, reflex irritation, sensitive skin, or seborrhoea, etc.). In my own clinic it is used as a routine in all eye injuries and all cases of facial burns in which the eyes are involved.

5. *Culture.*—A preliminary culture was taken from the conjunctival sac. The culture was repeated after 48 hours and if still positive was again repeated when the case was clinically better. The technique of culturing varies; the one employed in my series was advocated by Squad. Ldr. O'Connor, R.A.F.V.R., who did this part of the work for me. The culture was sown in nutrient broth (24 hours) and then resown on blood agar (24 hours). Too much reliance is not to be placed upon the results of conjunctival culture, and in estimating results the clinical picture was considered more important.

### Series I. Squad. Ldr. Sampson. Total Cases, 21

*1. Blepharitis.*—3 cases. All chronic, of many years' standing. Two showed *Staph. aureus* on culture; one was sterile at the end of treatment, which lasted 11, 7, and 10 days respectively. No recurrence for 2 months.

*2. Acute Conjunctivitis.*—5 cases (early, uncomplicated). Average duration of treatment, 4¼ days. The only organisms isolated were diphtheroids.

*3. Chronic and Recurrent Conjunctivitis.*—6 cases. Two were associated with seborrhoeic dermatitis, one with dacryocystitis. Average length of treatment, 8 days. 1 case unimproved by penicillin after 11 days and growing *Staph. aureus* was cured by sulphacetamide (albucid) in 3 more days.

*4. Phlyctenular Conjunctivitis.*—1 case. Cleared after 4 days. 7 weeks later there was a recurrence, which cleared after 3 days.

*5. Corneal Ulcer.*—3 cases. One showed no improvement after 4 days (no atropine). One cleared in 7 more days with atropine. The second ulcer failed to respond to 4 days of penicillin, but cleared after 5 days of sulphacetamide. (This was a case of rosacea, and recovery was considered not to be due to treatment.) Case 3 failed with sulphacetamide but cleared after 5 days of penicillin.

*6. Conjunctivitis of Socket.*—1 case. Complete cure after 10 days.

*7. Herpes Ophthalmicus.*—1 case. Recovery not accelerated by 15 days of treatment.

*8. Acute Meibomitis.*—1 case. 10 days' treatment, with clinical cure.

*Squad. Ldr. Sampson's Comments.*—(*a*) Blepharitis: Cases did better than they would with other forms of treatment. (*b*) Acute conjunctivitis: Penicillin is no improvement upon sulphacetamide. (*c*) Conjunctivitis of socket: An improvement upon other forms of treatment. (*d*) Herpes ophthalmicus: No improvement. He considers that the only condition which definitely does better with penicillin than other forms of treatment is blepharitis; otherwise sulphacetamide is as good.

### Series II. Squad. Ldr. Burr (and Others). Total Cases, 26

*1. Blepharoconjunctivitis.—7 Cases, All Bilateral*

| Culture | Days under Treatment | Result |
|---|---|---|
| (1) Sterile | 8 | Nearly normal |
| (2) Rt., sterile; Lt., haemophilus | 9 | Not improved |
| (3) Sterile | 5 | Improved |
| (4) Rt., Staph. albus; Lt., sterile | 12 | Normal |
| (5) Rt., non-haem. strep.; Lt., staphylococcus | 18 | Improved |
| (6) Rt., streptococcus; Lt., " | 11 | Improved |
| (7) Sterile | 2 | No result |

*2. Conjunctivitis, Acute.*—5 cases. Three cases with positive culture were treated for 10, 8, and 11 days. The first two were cured; the third (*Staph. albus*) grew worse in spite of treatment. Two other cases were sterile and were treated hourly. They were improved after 4 and 5 days respectively.

*3. Conjunctivitis, Phlyctenular.*—4 cases. Three were cured (11, 7, 9 days); 1 not improved (13 days).

*4. Corneal Ulcer.*—5 cases. Two grew *Staph. albus*; one unimproved in 3 days, the other healed in 7 days. Three other cases were sterile, and healed in 6, 9, and 2 days.

*5. Corneal Abrasion.*—1 case. Still some conjunctivitis after 5 days.

*6. Infected Socket.*—2 cases (sterile). Improved after 5 and 6 days.

Comments upon this series were not obtained, the work having been carried out by different observers owing to hospital changes.

### Series III. Squad. Ldr. Palin (and Others). Total Cases, 40

Owing to a change over of medical officers a detailed report is not available. The following table is a summary:

| Condition | | Average Response | Relapse Incidence |
|---|---|---|---|
| 1. Conjunctivitis | Acute | Very good | Nil |
| | Chronic | Good | Ratio 1:6 |
| 2. Blepharitis | Subacute | Very good | " 1:6 |
| | Chronic | " | " 1:4 |
| 3. Corneal ulcer | Infective | Good | " 1:5 |
| | Traumatic | Very good | Nil |
| 4. Keratitis | Superficial punctate | Indefinite | Ratio 1:6 |
| | Other forms | Poor | ? |
| 5. Impetigo of lids | | Fair | ? |
| 6. Dacryocystitis | | Good | Nil |

*Squad. Ldr. Palin's Comments.*—The majority of cases treated were: (*a*) acute conjunctivitis; (*b*) chronic conjunctivitis; (*c*) chronic blepharitis. Results in Group *a* were truly dramatic, complete subjective and objective cure being achieved in 6 cases within 24 to 48 hours; in these cases the organisms were pneumococcus and/or *Staph. aureus*. In Group *c* some of the "chronics" were themselves amazed at finding a degree of improvement they had not experienced in years of different treatments. One case of dacryocystitis demands special mention. After dacryocystorhinostomy the wound did not heal, and 10 days after operation was still gaping and discharging pus (with fistula formation). Treatment with penicillin was instituted, and within 72 hours the wound edges were completely and cleanly united and the fistula closed.

### Series IV. Squad. Ldr. Milner. Total Cases, 57

*A. Blepharitis. 16 Cases. Approximate Dosage, 280 Units a Day*

| Type | Culture | Culture Sterile (Clinically Clear in Days) | Total Dose (Units) |
|---|---|---|---|
| 1. Recurrent ulcerative | S. aureus | 5 | 1,400 |
| 2. Uniocular ulcerative | " | 7 | 1,960 |
| 3. Recurrent ulcerative with stye | " | 5 | 1,400 |
| 4. Associated with sycosis barbae | " | 4 | 1,120 |
| 5. Ulcerative: right eye | Sterile | 3 | 840 |
| " left eye | " | 7 | Treated with albucid 10% |
| 6. Ulcerative | S. aureus | | |
| 7. Ulcerative, associated with C.S.O.M. | S. albus | 7 | 1,960 |
| " " " right eye | Sterile | 10 | 2,800 |
| " " " left eye | " | 15 | Treated with albucid 10% |
| 8. Mild ulcerative | S. aureus; S. albus | 2 | 560 |
| 9. Squamous associated with rhinitis | " | 7 | 1,960 |
| 10. Squamous associated with eczema of pinna and running ear | S. aureus | 3 | 840 |
| 11. Squamous associated with seborrhoea capitis | S. albus | 8 | 2,240 |
| 12. Ulcerative (very chronic and present for years) | S. aureus; B. Morax-Axenfeld | 7 | 1,960 |
| 13. Ulcerative (very chronic and present for years; no treatment ever of benefit) | S. albus | 10 | 2,800 |
| 14. Chronic ulcerative | S. aureus | 10 | 2,800 |
| 15. Ulcerative. Recurrence of Case 5. This eye had been treated with albucid 10% | " | 6 | 1,680 |
| 16. Squamous | S. albus | 6 | 1,680 |

*B. Conjunctivitis. Acute, 8 cases; Subacute and Chronic, 16 Cases*

| Type | Culture | Sterile or Clinically Clear | Total Dose (Units) |
|---|---|---|---|
| **Acute: Approximate Dose, 280 Units a Day** | | | |
| 1. Catarrhal | S. aureus | 7 | 1,960 |
| 2. Traumatic, mucopurulent | ,, | 2 | 560 |
| 3. Catarrhal | Sterile | Not improved | 1,960 |
| 4. Traumatic, with ectropion | ,, | ,, | 1,960 |
| 5. Mucopurulent | ,, | 6 | 1,680 |
| 6. Catarrhal | Non-haem. strep. | 6 | 1,680 |
| 7. Mucopurulent | S. albus | 4 | 1,120 |
| 8. Mucopurulent (burns with cicatricial ectropion) | ,, | Dose not recorded (see below) | |
| **Subacute and Chronic: Approximate Dose, 250 Units a Day** | | | |
| 9. Catarrhal | Sterile | 1 (after other treatment for 4 days had failed) | 250 |
| 10. Chronic socket | ,, | Not improved in 7 days | 1,750 |
| 11. Chronic recurrent allergic | ,, | Not improved in 7 days | 1,750 |
| 12. Catarrhal associated with sinusitis | ,, | Not improved in 7 days | 1,750 |
| 13. Catarrhal | ,, | 2 | 500 |
| 14. Hyperaemia | ,, | Not improved in 2 days | 500 |
| 15. ,, | ,, | Not improved in 2 days | 500 |
| 16. Mild (some weeks' duration) | ,, | 2 | 500 |
| 17. Catarrhal, subacute | S. aureus | 2 | 500 |
| 18. ,, ,, | Non-haem. strep. | 6 | 1,500 |
| 19. ,, ,, | Sterile | 6 | 1,500 |
| 20. ,, ,, | ,, | 3 | 750 |
| 21. Mild rt. eye, with chalazion lt. eye / Rt. eye / Lt. eye | S. aureus / ,, | 2 / 4 | 500 / 1,000 |
| 22. Mild palpebral (allergic) | Sterile | Not improved in 3 days | 750 |
| 23. Mild palpebral | ,, | Not improved in 3 days | 750 |
| 24. Chronic | S. albus | 8 | 2,000 |

*C. Keratitis and Corneal Ulcers. 10 Cases. Approximate Dose. 250 Units a Day*

| Type | Culture | Sterile or Clinically Clear | Dose |
|---|---|---|---|
| 1. Phlyctenular | Sterile | Not improved after 10 days | 2,500 |
| 2. Dendritic | ,, | Not improved after 7 days | 1,750 |
| 3. Marginal, with conjunctivitis | ,, | 3 | 750 |
| 4. Exposure keratitis (burns) | S. albus | Dose not recorded. Inflammation and ulceration kept in check until plastic operation possible | |
| 5. Rosacea keratitis with ulceration | ,, | Not improved after 7 days | 1,750 |
| 6. Marginal | Sterile | Not improved after 3 days | 750 |
| 7. ,, | ,, | Not improved after 3 days | 750 |
| 8. Dendritic | ,, | Not improved after 5 days | 1,250 |
| 9. Marginal | ,, | Some improvement after 4 days | 1,000 |
| 10. Disciform keratitis | ,, | Not improved after 4 days | 1,000 |

*Comment on Group A.*—All cases showed great improvement after treatment with penicillin. Cases 12 and 13 had had chronic blepharitis for years; Case 13 was particularly bad, with brittle malplaced lashes (though no trichiasis). After three days both these patients were emphatic that their eyes had not been so comfortable for years.

*Comment on Group B.*—Acute conjunctivitis has been uncommon in my Service experience of four years; when it occurs it is usually of the catarrhal variety, and purulent or mucopurulent conjunctivitis is very uncommon. Thus I have not had the opportunity of using penicillin in bad cases. In catarrhal or mildly mucopurulent cases with a positive culture it undoubtedly is effective. Where the culture is sterile I doubt if it is more effective than other methods of treatment. The advantage of its use in such cases would be to maintain the sterility of the conjunctival sac while healing and recovery were taking place. In chronic conjunctivitis, unless definitely due to a low-grade infection, I doubt the efficacy of penicillin. So many chronic conjunctivitis cases have a very obscure aetiology: I associate many of them with reflex irritation, allergy, metabolic derangements, skin disorders, etc.—in which the condition is more a hyperaemia than an inflammation—and in these cases there was no response to penicillin, as would be expected. In cases of burns penicillin is of very great value. Conjunctivitis occurs in facial burns, and as the lids begin to contract into ectropion the conjunctivitis gets worse in spite of treatment, and exposure keratitis is almost a certainty. The eye is usually too irritable for a contact lens, and the lid margins too friable (or the pull of the ectropion too great) for a tarsorrhaphy to be successful. By keeping the conjunctival sac sterile with penicillin the eye can be protected from infective sloughing ulcers until the case is ready for plastic repair. Case B 8 and Case C 4 are examples. I am quite sure that but for penicillin one eye would have been lost or so severely damaged by corneal involvement as to be useless in each of these cases. All burns which even remotely involve the eye now have routine penicillin treatment—250 units a day in each eye.

*Comment on Group C.*—The only infective type of ulcer in this series was Case 4, which has been referred to above. (N.B.—I have seen only 4 cases of severe corneal ulceration during 4 years at an R.A.F. hospital.) Penicillin would seem to be of little value in herpetic keratitis or marginal ulceration.

*D. Dacryocystitis (Chronic).*—One case: profuse growth of *Staph. albus* and Koch-Weeks bacillus. Sterile in 8 days. Approximate dose, 2,000 units. In this case penicillin was injected into the sac, which was afterwards successfully operated upon.

*E. Trachoma (Old).*—One case. *Staph. aureus*—4 days—1,000 units. This was a case of old trachoma, and it seemed to be a secondary infection with no active disease. This contention proved correct, as the eye cleared up rapidly under penicillin.

*F. Episcleritis.*—One case. Sterile—4 days—1,000 units. This case had recurrent episcleritis in one eye and had already been treated by me twice for severe recurrences. On the third occasion penicillin was tried for experimental purposes, and the nodules disappeared very rapidly. This has happened on a second occasion. It seems here again, by keeping the conjunctival sac sterile, penicillin aids the eye to heal more rapidly.

*G. Folliculosis.*—One case. Sterile—no improvement in three days—750 units.

*H. Injuries.*—Penicillin is used as a routine in all cases of corneal foreign bodies and abrasions. Three perforating injuries have been seen during the period covered by this report, but in all cases the damage was extensive and the eye had to be removed. I have not yet had the opportunity of using the drug in conjunction with an intraocular operation or penetrating injury where the eye could be saved.

## Summary

*1. Dosage.*—In the strength used by us (drops, 500 units per c.cm.; ointment, 100 units per gramme) penicillin would appear to retain its potency for 4 hours (drops) and 6 hours (ointment). Frequency of treatment can thus be regulated according to the requirements of the case: very frequent applications of penicillin would seem unnecessary.

*2. Indications for Use.*—All observers are agreed that penicillin affords the best results in blepharitis; most of us would add acute conjunctivitis, but I have already indicated the small number of cases of acute infective conjunctivitis that occur under Service conditions—at least, in my experience. I do believe that in civilian practice, particularly in the hospital out-patient departments, penicillin will be the treatment of choice in these cases. The same remarks apply to corneal ulcers (infective). In chronic dacryocystitis I believe also it will become habitual to use penicillin preliminary to operation, but the cases seen have been too few for further comment. Recurrent styes and infected chalazion seem to be limited by applying penicillin, particularly in the intervals between recurrences.

As certain indications for penicillin I would add to the above (1) all cases of serious injury to the eye, whether penetrating or not; (2) all cases of facial burns involving the eye; (3) routine post-operative treatment.

It is impossible to assess the value of the drug in cases of injury, because there is no control for comparison. I have not yet had sufficient cases of penetrating injury to conclude whether the incidence of sepsis is less than before penicillin was employed. This is a matter requiring further investigation. Nor have I any evidence that non-infected cases heal more quickly with penicillin. Nevertheless I would advocate its use.

There remain a large assortment of cases in which penicillin has been used with doubtful or conflicting results. Chronic conjunctivitis seems to respond slightly, and the consensus of opinion is, I think, that penicillin is not of much value. Here I would repeat what I have mentioned above—that where a secondary infection with a penicillin-sensitive organism is also present, by inhibiting the growth of such an organism the drug may indirectly aid and accelerate healing. This statement applies to many inflammations which are, *per se*, unaffected by penicillin—such as episcleritis, trachoma, phlyctenular keratitis, marginal ulceration, herpetic keratitis, and many others.

Two observers in this series have been struck by the benefit obtained with penicillin in cases of infected socket. I have been impressed, in a series of 6 cases (seen outside the date range of the report), by the inefficacy of the drug. I found after some experimentation that 2½% red prontosil was much more effective. There are therefore some types of ocular inflammation which require much more extensive investigation before we can be sure how much to expect from the use of penicillin.

With regard to recurrence of inflammation I can say little yet. Because cases of one's own have not returned does not mean that there have been no recurrences; the patients may have gone to another part of the country. My opinion is that penicillin, being bacteriostatic and not bactericidal, will have little power to prevent recurrences unless it can be used, more or less as a routine, in intervals between exacerbations.

Finally, it must be remembered that many ocular inflammations are secondary to, or at least run parallel with, other affections—e.g., blepharitis and seborrhoeic dermatitis, conjunctivitis and rosacea, etc. The treatment of the underlying condition must not be lost sight of in the enthusiasm of employing a new method.

*Synopsis of Indications*

| | | |
|---|---|---|
| Definite | (*a*) Blepharitis | Acute and chronic Infective |
| | (*b*) Acute conjunctivitis | " |
| | (*c*) Corneal ulcer | " |
| | (*d*) Dacryocystitis | " |
| | (*e*) Styes, chalazion | Recurrent Prophylaxis |
| | (*f*) All ocular injuries | " |
| | (*g*) Facial burns | " |
| | (*h*) Immediate post-operative | " |
| Doubtful | (*a*) Chronic conjunctivitis | |
| | (*b*) Infected socket | |
| | (*c*) Other external inflammations, with a possible secondary infection | |

I believe penicillin to be quite useless in cases of deep keratitis, iritis, or cyclitis.

In conclusion I should like to emphasize the desirability of those concerned ensuring that all cases of facial burns with ocular involvement be given penicillin *from the very beginning of treatment*. In such a way I believe a number of ulcers from exposure keratitis can be avoided.

My thanks are due to Air Cdre. P. C. Livingston for making possible the supply of penicillin; to Squad. Ldrs. Sampson, Burr, and Palin for their co-operation, and for supplying me with their reports; to Squad. Ldr. R. J. O'Connor for the bacteriological culture work; to Squad. Ldr. W. I. Leslie for conducting experiments upon the time potency of penicillin; and to Sister M. C. E. Lodge for carrying out exact lines of treatment in my series of cases, thus ensuring uniformity of results.

## PENICILLIN AND SULPHONAMIDES IN INFANTILE GASTRO-ENTERITIS

BY

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The high incidence of acute gastro-enteritis in infants (familiarly known as D. and V.) continues to give cause for anxiety, showing a definite upward trend on the evidence of the figures of deaths from enteritis and diarrhoeal diseases in those under 2 years, which in England and Wales for 1939 to 1943 were: 2,812, 2,891, 2,985, 3,415, and 3,518 respectively. A disease predominantly of the hot months (hence the name summer diarrhoea) in the period before the first world war, it now shows no particular seasonal predilection except a tendency to increased severity and perhaps also increased prevalence during the period when catarrhal colds are rife, in the late winter and early spring months. In the absence of general notification (which should be made compulsory and be limited to the first year of life) estimates of the real incidence can only be conjectural, while mortality figures tend to be vitiated by inaccurate or incomplete certification, as exact diagnosis is not always easy in the absence of definite knowledge of the essential aetiology. Despite arguments to the contrary, there are no valid grounds for considering this disease to be different from so-called neonatal diarrhoea, except for such differences as are attributable to the physiological characteristics of young babies. Workers in this field have recently inclined to the view that invasion of the upper respiratory tract, due most probably to a virus or group of viruses, is the primary cause, and the damage to the mucous membranes thereby sustained renders them more vulnerable to the ordinary bacterial flora of that region; whether the virulence of organisms harboured before attack may be enhanced in the process has not been definitely established. A somewhat similar process may occur in respect of the normal intestinal bacteria, notably coliforms and enterococci; nor should it be forgotten that the same primary organism (causing identical disease processes so far as can be determined clinically) may gain entry by either the gastro-intestinal or the upper respiratory tract, as has been proved in poliomyelitis.

The five recent cases described here, though representative, naturally belong to the severer form of the disease, which may range from the mildest grades, in which evidence of toxi-infective processes may be minimal or absent, to fulminating attacks. It is a matter of experience that the latter may sometimes respond to treatment more swiftly and completely than certain intermediate grades, the crucial difference apparently being the presence or absence of an infective focus and the success or failure of the measures employed to eradicate or neutralize it. All five cases were treated in single-bedded rooms (technically termed cells and often erroneously referred to as cubicles) in the same isolation unit and attended by the same medical and nursing staffs, with strict observance of aseptic nursing technique, including the wearing of "Cestra" type masks.

### Management of Cases

To avoid unnecessary repetition, an outline of the management of the cases is given at this stage. A complete history of the patient from birth and the recent history of immediate contacts are followed by weighing of the patient and restoration measures such as warmth and fluids by mouth; if dehydration is present an intravenous infusion of Hartmann's solution is given supplemented by 5% glucose at once or after a few hours and by 4 parts solution to 1 part serum or plasma (the latter occasionally causes febrile reactions which may mislead) according to severity of symptoms and duration of disease, until metabolism is restored to normal as checked by level of plasma bicarbonate, proteins, urea, and chlorides, and by blood transfusion as shown by haematocrit readings and blood-count determinations. With experience these examinations may often be dispensed with, but avoidance of anaemia and oedema is best secured by periodic tests. The duration of the drip may vary from 1 to 5 days—average 3 days. Swabs of throat, nose, and nasopharynx (the most important site of the three) and specimens of faeces and urine are taken on admission and repeated as considered necessary. If vomiting persists only sips of Hartmann's solution or boiled water are given; but if it has ceased, increasing quantities are taken orally, deducting the amount from the drip intake. In 24 to 72 hours feeding is resumed, starting usually with a 1 in 4 dilution of a full suitable for the age, rapidly reaching full strength according to appetite and tolerance: some infants can take only a 1 in 4 solution, while others can stand a 1 in 2 or even full-strength mixture from the outset, the remainder of fluid being given between feeds if the prescribed volume based on body weight is refused at the usual feeding-times. If there is no contra-indication the food given before attack is chosen; if it was thought to disagree with the patient humanized national dried milk is the food of choice, and rarely requires modification such as citrated, peptonized, or acidified milk. Occasionally "Secway" may be needed to bridge the period between fluids and feeds. Difficulty at this stage is nearly always attributable to an infective focus, usually in the middle ear, occasionally in the renal pelves; and a sulphonamide, commonly sulphamezathine or sulphathiazole, is given either in the drip or orally with a view to preventing or even to securing resolution of the inflammatory process. Success is conditioned by the susceptibility of the causative organism, the natural resistance of the patient (specific immunity may likewise be a factor), and the nature and timing of such operative procedures as are adopted. Proper timing is considered of vital importance.

harm may be caused by premature operation as positively as by inadequate or tardy intervention.

The essential data, with critical comments, are given for each case in chronological order.

### Case I

W. G.; 5/12 M., weight 15 lb. 4 oz., artificially fed. May 21, 1944: Onset—stools relaxed and green. Admitted 4th day; T. 100.6° F. Moderate dehydration present; intravenous Hartmann's solution on following day with plasma later, and next day bilateral myringotomy, revealing sero-sanguineous exudate; bilateral cortical mastoidectomy 12 hours later; mucous membrane of the mastoid cells was inflamed and bone soft and red; no definite pus found. Wounds were stitched, leaving fine drainage-tube at lowest part for introduction of dilute penicillin (400 units per c.cm.) every 6 hours for 5 days; complete healing followed in 9 days. Throat and nasopharynx—*Staph. aureus, M. catarrhalis,* and coliforms; nose—*Staph aureus*; right ear—*M. catarrhalis, Staph. albus*; left ear—no growth; mastoid bone—no growth.

*Treatment.*—Sulphathiazole 6 g. in 4 days on admission, and sulphamezathine 12 g. in 7 days, starting 5 days later. The patient did not improve—fever, diarrhoea, and loss of weight persisting despite four drips (three intravenous, one tibial marrow) and one blood transfusion (raising haemoglobin from 62 to 84%). A trace of protein, some pus cells and red cells, and *Staph. aureus* and enterococci appeared in the urine at this stage (catheter specimen). Reopening the mastoids was considered unwarranted. Blood culture taken shortly before death on the 27th day of the disease revealed numerous *Staph. aureus,* partially sensitive to sulphonamides.

*Necropsy.*—Left mastoid—mucoid material; right—frank pus present, bone soft; from both, *Staph. aureus* and coliforms were isolated. Right middle cerebral vein thrombosed with purulent exudate along course.

*Comment.*—Both myringotomy and mastoidectomy were probably undertaken too early; a more generous and longer course of sulphonamides advisable; mastoids might have been reopened with benefit. Coexisting renal damage may mislead, but appearance of pathogens in urine should suggest taking a blood culture.

### Case II

B. W.; 6/12 M., weight 14 lb. 15 oz., artificially fed. May 24, 1944: Onset with fever, loose green stools, and bronchitis, for which sulphamezathine 9 g. in 4 days was given. A week later vomiting and continued diarrhoea led to dehydration; corrected by intravenous Hartmann's solution with glucose and plasma for 5 days and a second course of sulphamezathine 15 g. in 5 days, of which 6 g. was by the intravenous route; protein (a trace), scanty pus cells, and coliforms appeared in urine in the course of this treatment. Three weeks after onset bilateral myringotomy revealed muco-pus on both sides, containing *Staph. aureus.* No improvement followed, and cortical mastoidectomy was performed next day; the bone was softened and muco-pus was present in the mastoid cells, but cultures taken at operation proved negative. Fever continued, and blood culture taken 4 days after operation was found to grow penicillin-sensitive *Staph. aureus* scantily. Penicillin 40,000 units every 24 hours was given by intravenous drip for 6 days and 5,000 units 3-hourly for an additional 2 days, when fever had just gradually subsided to normal. Blood culture was sterile on the day after starting penicillin therapy, which was continued to prevent relapse. As the penicillin-tube opening was still patent 13 days after operation and discharged mucopurulent material, reopening of the right mastoid was considered, but was deferred until rise of temperature or other sign of inflammation indicated; but subsequent recovery was rapid and uneventful.

*Comment.*—The negative bacteriological findings are possibly due to sulphonamide present in the swab material, para-aminobenzoic acid not being added to the culture media. The presence of renal complications did not seem to influence the course of the disease. Timely blood culture and use of penicillin saved the patient.

### Case III

M. P.; 5/12 F., weight 11 lb. 11 oz., artificially fed. May 24, 1944: Admitted with history of watery, green, offensive stools for 6 days, preceded by cough and nasal discharge; mild dehydration; T. 98.6° F. The upper respiratory tract revealed nothing noteworthy apart from *Str. viridans* in the nasopharynx; urine normal. Some improvement followed a course of sulphamezathine, but 10 days later fever recurred with diarrhoea and pronounced dehydration, requiring an intravenous drip with plasma. Bilateral myringotomy 2 days afterwards yielded watery exudate containing *Staph. albus* and coliforms on the right side and blood only (sterile) on the left side. No improvement ensued, and a plasma drip followed by blood transfusion (haemoglobin raised from 75 to 95%) was needed to sustain life. A second bilateral myringotomy gave a dry result, but mastoidectomy 4 days later revealed frank pus and necrosed bone (left) and soft readily bleeding bone (right), both sterile on culture. The blood was also sterile. With local penicillin healing of the wounds took place in 10 days. Some fever continued for 5 days after operation, but thereafter gain of weight and general progress were satisfactory.

*Comment.*—The negative bacteriological findings may have been due to sulphonamide either in the tissues killing the organism or on the swab inhibiting growth. Efficacy of mastoidectomy difficult to assess in such cases, although subsidence of fever is suggestive.

### Case IV

P. L.; 8/12 F., weight 11 lb. 11½ oz., artificially fed. June 10, 1944: Onset sudden, with copious vomiting and loose, yellow, offensive stools; moderate dehydration; temperature 99.6° F. On admission bilateral myringotomy: left, sero-pus; right, blood only; both yielding *Staph. albus.* Upper respiratory tract revealed nothing of note apart from pneumococci in nasopharynx. Fever subsided for 3 days, when it recurred, necessitating an intravenous drip with plasma and 3 days later 100 c.cm. blood, raising haemoglobin from 73 to 98%. The urine was found to contain protein, numerous epithelial and pus cells, and scanty red cells; *B. coli* and *proteus* were found on culture. Blood culture was sterile. Fever and symptoms subsided in 3 days on a course of sulphathiazole, 10 g. in 6 days, and remained settled. A month later the urine still contained *B. coli* on culture, and a trace of albumin; otherwise recovery appeared to be complete.

*Comment.*—Pyelitis seemed to be the sole cause of the gastro-enteritis, responding rapidly to sulphonamide, but it may be merely a complication.

### Case V

R. B.; 2/12 M., weight 6 lb. 9 oz., breast-fed for first 3 weeks. June 23, 1944: Cough and diarrhoea; general condition satisfactory. Admitted a week later with vomiting and frequent green, watery motions but without gross dehydration. Next day condition worse, requiring an intravenous drip. Throat and nose yielded *Str. viridans, M. catarrhalis,* and coliforms; nasopharynx—*Staph. aureus* and pneumococci; urine—trace protein, epithelial cells, *B. coli,* and *proteus.* Two days later myringotomy revealed a small amount of mucoid pus (right) and serous fluid (left), both containing *Staph. aureus* and *albus,* pneumococci, and coliforms. As high fever continued sulphamezathine 9 g. in 4 days was given, and re-myringotomy was done 5 days later, again yielding small amounts of muco-pus and the same bacteria as before. Blood culture next day gave pneumococci Type 8 in uncountable numbers, sensitive completely to penicillin and partially to sulphonamide. Penicillin therapy, 5,000 units 3-hourly intramuscularly, was started, giving a level next day of ± 1-8 after 3 hours, and the dosage was reduced to 4-hourly intervals. The patient seemed better and took feeds readily, but 2 days later a generalized convulsion and meningitic signs appeared; lumbar puncture showed purulent fluid containing numerous pneumococci on culture. No response followed 3 injections of 5,000 units of penicillin given intrathecally at 8-hour intervals, and the patient died 24 hours later.

*Necropsy.*—Inspissated pus in both middle ears and mastoid cells. Greenish-yellow pus over entire surface of the brain, with subarachnoid haemorrhage over the base.

*Comment.*—Sulphonamide was given too late in the disease to be effective; blood culture and lumbar puncture undertaken too late; penicillin probably sterilized the blood (a second culture was not taken, as the physical state was poor) but failed to prevent spread to the meninges, which very likely had taken place some hours or days before the convulsion which led to lumbar puncture.

### Discussion

The cases recorded above illustrate well the difficulties encountered in locating the infective focus as well as in deciding the measures best calculated to eradicate it and the appropriate time to apply them. Although a history of cough or other symptom of respiratory infection was present in three cases the clinical evidence of such infection was negligible. While pyelitis occasionally appears to be solely responsible for gastro-enteritis, renal infection indistinguishable from mild pyelitis may occur at any stage of an attack, due primarily to upper respiratory infection, and should suggest the existence of bacteriaemia or septicaemia originating in mastoid suppuration. All three mastoidectomies were carried out under local anaesthesia, using 1% novocain preceded by 1/4 gr. seconal. With careful infiltration pain is absent or minimal; usually the patients suck their bottles contentedly during the operation. It seems warranted to conclude that, provided other possible causes are excluded, no patient suffering from gastro-enteritis should be permitted to die without operation; if properly prepared for it with intravenous fluids, preferably including human serum or plasma, untoward effects are rare, and benefit some-

times appears to accrue in cases in which evidence of mastoiditis was equivocal at the time of operation. The necessity for operation is governed by persistence of fever, diarrhoea, and/or vomiting and loss of weight despite every effort at resuscitation; the appearance under observation of enlarged posterior cervical glands gives support to the diagnosis, but neither their presence nor their absence should influence the final decision to operate.

There is general agreement that sulphonamides often fail to prevent the onset of mastoiditis and may actually be dangerous in masking the disease. Whether penicillin will succeed where sulphonamides have failed has not been adequately explored, but the present limited experience furnishes grounds for the hope that timely use of the drug will reduce appreciably the high case-fatality of infantile gastro-enteritis.

**Summary**

Five cases of severe acute gastro-enteritis in infancy, with two deaths, are described; in three patients mastoidectomy was performed, resulting in (*a*) rapid resolution of suppurative processes found to be sterile at operation; (*b*) recovery from staphylococcal septicaemia cured by penicillin; (*c*) death from staphylococcal septicaemia uninfluenced by sulphonamides. Of the remaining two cases one patient with *B. coli* pyelitis improved rapidly with sulphathiazole while the other died from pneumococcal meningitis and septicaemia, not responding to sulphonamide or penicillin therapy.

Our grateful thanks are due to Dr. R. Cruickshank, who carried out the bacteriological examinations, and to Miss Winifred Hall, who undertook the otological work.

# A SEVERE HAEMOLYTIC TRANSFUSION REACTION DUE TO THE Rh FACTOR

BY

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The demonstration of the Rh factor in human blood cells (Landsteiner and Wiener, 1940) has led to the elucidation of many previously unexplained haemolytic reactions following the transfusion of apparently compatible blood. Later workers (Levine *et al.*, 1941; Boorman *et al.*, 1942; Race *et al.*, 1943) have shown that the antibody responsible for the haemolysis may develop in an Rh-negative person either as a result of previous transfusions with Rh-positive blood or, in the case of women, as a result of bearing an Rh-positive foetus. In the latter case the infant usually suffers from haemolytic disease of the newborn. In the present case a severe haemolytic reaction followed the transfusion of Rh-positive blood in a woman who had previously been transfused (probably with Rh-positive blood) and also had borne several Rh-positive children. It is not known which of these two factors was responsible for the production of the antibody.

## Case Record

Mrs. A., aged 38, had a history as follows:—1929: Forceps delivery; normal baby, Group $A_2$ Rh-positive. 1932: Normal delivery, but retained placenta; baby healthy at birth but died at 5 months; cause unknown. 1936: Normal delivery followed by post-partum haemorrhage. Was given blood transfusion (group not known). Baby healthy; Group O Rh-negative. 1940: Normal delivery. This child, who is Group $A_2$ Rh-positive, was said to have been jaundiced for four weeks after birth. 1942: Twins. First infant stillborn owing to hydrocephalus; second infant healthy, Group $A_2$ Rh-negative. Labour followed by severe haemorrhage. Two transfusions of Group A blood were given, with an interval of 14 days; both were followed by severe rigors.

In 1944 she was seen when 22 weeks pregnant. Urine and blood pressure were normal. In view of a moderate anaemia (Hb 55%, R.B.C. 3,600,000) it was decided to give her a blood transfusion. One pint of Group A blood was administered. One hour later she started to vomit, her pulse became weak, and she complained of lumbar pain. Anuria set in and alkali therapy was begun immediately. The following morning she was jaundiced. The daily urinary output for the next six days varied between 1 and 4 oz. The urine was dark red in colour and was loaded with albumin. On the fifth day she complained of severe headache, and the next day some oedema of the legs was noticed. On the eighth day normal diuresis set in and her condition gradually improved. On the thirteenth day she left hospital against advice, but had apparently recovered from her haemolytic reaction. The following day she returned with an incomplete abortion. The placenta had to be removed under general anaesthesia. She collapsed before the operation, but rallied sufficiently for it to be completed. She died four hours later, apparently from shock.

A necropsy was performed 24 hours after death. Apart from signs of shock, the significant findings were those related to the haemolytic transfusion reaction. The liver showed signs of fatty change. The kidneys were enlarged to twice their normal size and showed a pale-grey colour with an indistinct cortical pattern. The spleen was greatly enlarged (580 g.) and firm. The abdominal lymph glands were also enlarged.

Microscopical examination of the kidneys revealed the characteristic lesions of "transfusion kidney" as described by previous workers (De Gowin *et al.*, 1938; De Navasquez, 1940). The organ differed from that in average cases in having numerous focal collections of lymphocytes, macrophages, and eosinophils in both cortex and medulla. Similar changes have, however, been described by Goldring and Graef (1936) and by Ayer and Gauld (1942). The liver showed fatty change and slight degeneration towards the centres of the lobules. The spleen, in addition to siderosis, showed marked proliferation of the histiocytic cells of both the pulp and the Malpighian bodies. The abdominal lymph glands presented a similar picture.

## Comment

The patient's blood was examined on the 2nd and 12th days after transfusion. The donor was Group A Rh-positive. The patient was Group A Rh-negative, and on the first examination, two days after transfusion, no agglutinable Rh-positive cells were found, indicating that all the transfused cells had been destroyed. On this occasion Rh antibody was demonstrable in the undiluted serum. On the 12th day the Rh antibody titre had risen from 1/1 to 1/8. The husband was found to be Group $A_2$ Rh-positive; the blood groups of the children have already been given.

An interesting problem in this case is which of the various possible factors was responsible for the production of Rh antibody. Of the patient's four surviving children two are known to be Rh-positive. It is stated that one of these—the third—was jaundiced for four weeks after birth, and it is probable that this was due to haemolytic disease of the newborn; the absence of signs of haemolytic disease in the case of the fourth child would be due to its being Rh-negative. It is therefore at least possible that the production of Rh antibody may have been due to repeated pregnancies. The Rh group of the blood given in the earlier three transfusions is not known, but on probabilities it is likely that most, if not all, were Rh-positive. Also the fact that the second and third were followed by reactions is suggestive. The other interesting feature is the remarkable size and reaction of the spleen. There was no evidence of leukaemia in a blood count done shortly before the last transfusion, and neither the necropsy findings nor the histology indicated reticulosis.

We believe that the reticulo-endothelial hyperplasia in the spleen was the result of stimulation by incompatible transfusions; probably two transfusions in 1942 and certainly one a fortnight before death.

**Summary**

A case is described of a severe haemolytic reaction following the transfusion of Rh-positive blood into an Rh-negative woman who had borne two Rh-positive children and had previously had two transfusions. It is not known which of these two possible factors gave rise to the Rh antibody.

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# Medical Memoranda

## Treatment of Cerebral Malaria

During recent months certain contributions on malaria have appeared in the *Journal* which have apparently been written by authors with limited experience of this disease. Although these contributions have added little or nothing to existing knowledge, they have in the main been helpful to those who are encountering malaria for the first time. This cannot be said of the article by Surg. Lieut. Sneddon (*Journal*, 1943, **2**, 814), reporting a fatal case of cerebral malaria, in which the commentary on treatment is seriously misleading.

### DOSAGE OF QUININE

The author records the administration of intravenous quinine in a dosage of 10 gr. daily, and comments that this dosage was higher than the 5 to 7 gr. daily advocated by Manson-Bahr (1942), leaving the impression with the reader that 10 gr. daily should be adequate for the treatment of cerebral malaria. It may be useful to present in tabular form the recommendations of various authorities on the optimum dosage of quinine in that disease.

| Authority | Preparation | Initial Dose | | Subsequent Dosage Indicated | |
|---|---|---|---|---|---|
| | | gr. | Route | Amount (gr.) | Route |
| Field (1938) | Quinine dihydrochlor. | 7½ | I.V. | 10½; up to total of 30 in 24 hours | I.M. |
| | | 10½ | I.M. | | |
| Manson-Bahr (1940a) | " | 10 | I.V. | "Free and frequent administration of quinine" | Not stated |
| Manson-Bahr (1940b) | " | 15 | I.V. | Not stated | — |
| Manson-Bahr (1942) | " | 5–7 | I.V. | 5–7 daily | I.V. |
| Napier (1943) | Quinine dihydrobrom. | 10 | I.V. | Repeat 10 gr. a few hours later; intravenous therapy may be needed for 2 days | I.V. |
| Nocht and Mayer (1937) | Quinine dihydrochlor. | 7½ | I.V. | Not stated | — |
| | | 7½–15 | I.M. | | |
| Rogers and Megaw (1942) | Quinine dihydrochlor.* | 7½ | I.V. | " " | — |
| Stitt (1942) | Quinine bimuriate | 10 | I.V. | Not more than 30 in 24 hours | I.V. |

* Rogers advocates dihydrobromide.

It will be noted that the recommendations above are far from consistent. Though they may each have given satisfactory results in the particular conditions in which they were used, their diversity makes it difficult for the novice to decide on the correct line of treatment. In general it may be stated that the amount of treatment required will vary in inverse ratio to the amount of immunity possessed by the patient. Thus considerably larger doses of quinine may be required for the majority of Europeans and Americans, who usually possess little or no acquired immunity, than for patients living in endemic areas, who may possess partial immunity.

### RECENT RECOMMENDATIONS

Since the outbreak of the present war large numbers of Allied troops with attendant medical services have been deployed in highly malarious areas, providing an unprecedented opportunity for the study of malaria in general and of its neurological complications in particular. The following simple directions have been compiled from the most recent recommendations of the Allied Forces on the treatment of cerebral malaria, and are founded on the experience gained before and during the present war. They are applicable to any case occurring in the adult male.

Drug of choice: Quinine dihydrochloride.
Route: Intravenous.
Rate of injection: Very slow. Maximum speed 1 minute per grain; optimum speed, 2 to 4 minutes per grain.
Initial dose: 6 to 10 gr.
Dilution: Minimum, 6 gr. in 10 c.cm.
Diluent: Distilled water or normal saline if 10 c.cm. is used. Normal or glucose saline for larger quantities.
Subsequent dosage: 6 gr. 4-6 hourly, not exceeding a total of 30 gr. in 24 hours, or 10 gr. 8-hourly, until recovery from coma occurs and satisfactory oral administration is possible.

Intramuscular mepacrine as an adjuvant to intravenous quinine may give good results in the hands of those familiar with its use. I wish to emphasize the necessity for persevering with intravenous quinine in comatose cases even though the prognosis appears hopeless. This is well illustrated in a case reported by Whitehill (1943). Whitehill's patient was in coma for approximately 3½ days, excluding a lucid interval of 1½ days, and, although the coma was complicated by an acute malarial nephritis, recovery ensued after a total dosage of 75 gr. of intravenous quinine had been given.

### POINTS FOR COMMENT

There are two other points in Surg. Lieut. Sneddon's article which are worthy of comment:

1. *Use of Intravenous Salines.*—A not infrequent terminal event in cerebral malaria is pulmonary oedema, and caution should always be exercised not to give more intravenous saline than is necessary, and to give it slowly. The administration of fluids through a Ryle's tube passed into the stomach and connected to a drip apparatus has been recommended by Lieut.-Col. G. A. Ransome, I.A.M.C. (personal communication). It is advisable to nurse patients in a semi-recumbent position rather than dead flat, in order to prevent hypostatic congestion.

2. *Lumbar Puncture.*—This should be carried out as a routine in coma. A certain proportion of cases of cerebral malaria suffer from cerebral oedema with a raised C.S.F. pressure, and, in these, improvement may follow the judicious removal of C.S.F. Further, in malarious areas cases of cerebrospinal meningitis may suffer simultaneously from malaria. The dual pathology may here easily be missed unless a lumbar puncture is carried out.

In conclusion I would like to express my emphatic concurrence in Surg. Lieut. Sneddon's statement that if treatment is to be successful it must be prompt. More than any other factor in the management of the case, the prognosis in cerebral malaria depends upon the speed with which the diagnosis is made and treatment instituted.

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## Two Cases of Snake-bite

The following cases are recorded for the reason that snake-bite is an uncommon accident in this country and that it must be still more unusual for two patients to be bitten by the same snake. The great difficulty experienced in obtaining antivenene is also a matter for consideration.

### CASE HISTORIES

On May 18, 1944, two healthy boys—A. T., aged 12, and J. O., aged 14—were playing on an open heath when A. T. saw and caught hold of what proved to be an English viper (*V. berus*), commonly known as an adder, 24 in. long. The snake bit him and he dropped it, whereupon his companion gave chase and, having grabbed the snake, was also bitten a few minutes later. A. T., who received the first bite at 3.30 p.m., vomited immediately and felt so ill that he lay down on the grass, where he was found 20 minutes later by his schoolmaster, who stated that the boy was very pale and drowsy, was unable to walk, and complained of sore throat, pain in his abdomen and feet, and great thirst. He was vomiting. The bite was on the dorsum of his right hand, which was much swollen, with a dark-blue area surrounding the bite. The master incised the bite with a penknife sterilized in dettol, but very little blood flowed and it clotted immediately.

The boy was admitted to the West Suffolk Hospital, Bury St. Edmunds, at 5.30 p.m., in a condition of extreme shock. His colour was grey-blue, and he was cold, limp, and semi-conscious. Respiration was very shallow and the radial pulse was not palpable. Temperature was subnormal. He complained of thirst and sore throat. His right hand was swollen, shiny, and grey-blue in colour; there was no lymphangitis, but the axillary lymph glands were enlarged and very tender.

Nikethamide (coramine) and adrenaline were administered, and the usual measures for treatment of shock were taken. By 7.45 p.m. his general condition had considerably improved and he was complaining of pain in his hand and abdomen and of sore throat. Examination showed no haemorrhages in his skin or mucous membranes. Pulse 120 and of good volume; heart and lungs normal; abdomen somewhat distended, and tympanitic and tender; deep reflexes present. A puzzling sign was wide dilatation of both pupils with loss of light and accommodation reflexes. It was discovered subsequently that during the morning atropine had been instilled by an ophthalmic surgeon by whom he had been examined.

He was given 12 minims of nepenthe, and had a fairly comfortable night. On the 19th his general condition was much improved. The right arm, however, was swollen up to and beyond the elbow and was extremely tender. In the afternoon of that day a supply of antivenene was obtained through the Ministry of Health, but the boy was so much better that administration was withheld. On the 20th he complained more of sore throat and dysphagia, and a hot, red, and very tender oedema involved the whole of his right arm and shoulder and upper part of chest, back and front. 10 c.cm. antivenene was given intramuscularly at midday. On the 21st his general condition was much improved and there was no increase of the oedema. On this and the next day he developed extensive ecchymoses in the skin of his right arm and chest. There were no haemorrhages elsewhere, and his urine showed no red blood corpuscles. Recovery was subsequently uneventful, and he was discharged on May 30. His temperature had never risen above 100°.

The other patient (J. O.) was bitten on the outer side of the little finger of his right hand. Another boy promptly sucked the wound and tied a ligature round his arm. He developed no symptoms until 1½ hours later, when he vomited and complained of sore throat and difficulty in speaking. His right hand became swollen and painful.

He was admitted to hospital at 8 p.m. There were no signs of shock, but tender swelling and redness of his right hand, with marked lymphangitis and axillary lymphadenitis. The site was incised under gas anaesthesia and bled freely: a potassium permanganate dressing was applied. No other symptoms developed, and except for slight swelling of his finger he was well on May 22.

COMMENT

It is interesting to note that in this instance the viper did not discharge all its venom at the first bite.

The condition of the boy A. T. on admission was most alarming, and it is clear that antivenene as a life-saving measure would need to be administered within a few hours of the bite. Whether the dose given in this case prevented further oedema and lymphangitis is a matter for speculation. It proved impossible to procure antivenene through the usual channels, and the supply obtained through the good offices of the Ministry of Health was received only after nearly 24 hours' delay. It was prepared by the Pasteur Institute, Algiers, against the venom of the horned viper of Africa (*Cerastes cornutus*). Barrett (*Lancet*, 1934, **2**, 60) says: "As the minimum lethal dose of the adder venom for an adult is probably 50 mg. and the amount injected by a British adder is between 5 and 10 mg., the results are seldom grave, but in small children and invalids energetic measures are called for." Apart from first aid, these measures should be directed to the treatment of vasomotor shock and relief of pain.

Nevertheless, in the first of the two cases here described it would have been a great comfort to be in a position to give intravenous antivenene on admission, for the boy seemed likely to die.

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## Spontaneous Expulsion through the Rectum of a Kocher Forceps left in the Abdomen 14 Months

I could not find, in the literature in my hands, a case similar to the one recorded below, so I thought it might be interesting enough to merit publication.

CASE HISTORY

A woman aged 40 was admitted to the county hospital on Dec. 30, 1943, complaining of the existence of a piece of scissors in her anus. 14 months previously she had been operated upon for a tumour of the uterus in a maternity hospital elsewhere. She was told that she had a large tumour of the uterus, which was removed. Except for a mild swelling on the left lower extremity no complication had occurred and the wound healed completely. The patient was discharged from the hospital 45 days after operation. At home she was quite well for about 8 months, then she began from time to time to feel pains in the left lower quadrant of the abdomen. Shortly after the onset of these pains she developed intermittent diarrhoea and vomiting. Some 20 days before attending hospital she felt a hard substance in her anus and was unable to crouch and sit. Finally, 17 days later, she touched a part of a pair of scissors which came to the mouth of the anus, and after working hard for two days succeeded in expelling it. She failed to extract the other part. The extracted piece proved to be a branch of a Kocher forceps.

Examination revealed a poorly nourished woman, semi-ambulant and appearing ill, with a temperature of 99.8° F. The pulse was 104. There was an operation scar in the midline between the umbilicus and the symphysis pubis. Vaginal examination revealed a freely movable cervix but no corpus luteum. The fornices were free of masses or infiltration; the patient's menses had ceased since the operation. There was some slight tenderness and redness on the left side of the anus. On deep palpation rectally the other branch of the Kocher forceps could be felt; this was in an inclined position, so that the pointed end had plunged into the left ischio-rectal fossa. Under general anaesthesia the anus was dilated and the remaining branch of the forceps was extracted. After intervention the patient improved steadily and made a complete recovery.

The extracted piece was 14 cm. long, and formed a complete Kocher forceps with the part removed by the patient. Both pieces of this forceps were discoloured. After remaining 13 days under observation she was discharged home in excellent health.

COMMENT

A Kocher forceps left in the abdomen during a gynaecological laparotomy began to give rise to symptoms after nearly 8 months and travelled from the peritoneal cavity into the large intestine. The mechanism of this remarkable (and fortunate) migration is hard to explain. However, one may say with Jalaguier and Mauclaire (1893) that first the foreign body encysted and some adhesion occurred with the intestine: this was accomplished in 8 months. Then under the protection of these adhesions the perforation of the intestine took place and the migration started: this phase lasted 6 months.

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REFERENCE

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# Reviews

## CLINICAL SYPHILIS

*A Synopsis of Clinical Syphilis.* By James Kirby Howles, M.D., M.M.S. (Pp. 671; illustrated. 30s.) London: Henry Kimpton.

The appearance of this book is most opportune, partly because it is good on the whole, and partly because up-to-date monographs on syphilis are few. It is divided into three main sections: general considerations, systemic and regional syphilis, and familial and public health aspects. The first includes primary, secondary, latent, and tertiary syphilis, clinical and pathological diagnosis, treatment, and prognosis; the second, syphilis of the various organs and systems of the body, the treatment of each stage, organ, or system being given in the appropriate chapter. Section 3 is devoted mainly to congenital syphilis and syphilis in pregnancy; it includes the epidemiology of the disease and the organization of the syphilis clinic. In an appendix is a brief account of the history of the disease, and there is a long list of references.

The book is somewhat artificially arranged, but, as the author points out in his preface, the gain in clarity and the saving of space more than outweigh the obvious disadvantages. It can be said at once that, speaking broadly, this is a book which will be of great value to the syphilologist; it sets out the subject-matter with commendable clarity, experts are frequently quoted on debatable subjects, and there are numerous illustrations. Most of these are first-class, but some are hardly up to standard—e.g., Figs. 5, 6, and 9. Fig. 18, labelled "Pipestem lymphadenopathy [*sic*] of Dorsum of penis," shows what looks like a rather prominent dorsal vein, and Fig. 31 hardly represents what spirochaetes really look like under the dark-ground microscope; incidentally, it might have been useful if a more detailed account of how to set up and examine a dark-ground specimen had been included.

Here and there we find what seem to be rather important errors, such as (p. 152): "serologic test is of the greatest value from two weeks after the infection has occurred." Surely this should read, "after the appearance of the primary lesion." And on page 154, "report results as . . . doubtful (complete haemolysis)," should read, "*incomplete* haemolysis." In general the average reader would have been glad of a rather fuller section on false positive serum reactions. On page 256 occurs the word "seroprimary," which conveys to us no meaning at all; while on page 473 is the statement, "Organism (*Spirochaeta pallida*) . . . does not remain active, even under the most propitious conditions, for more than 48 hours"; this has been disproved by specimens which have crossed the Atlantic by ship several times and still retained their motility. These are a few shortcomings in an otherwise excellent account; it is the treatment described which lends itself most to criticism. Few modern syphilologists would agree with Plan A for early syphilis: why wait to start treatment till the first visit *after* the diagnosis; why not start at once, and why not start with an arsenical? On page 243 bismuth subsalicylate is described as oil-soluble, whereas on page 222 it is called a suspension, and the average weekly dose is 1 c.cm.—surely a very small one. The introduction of mercury rubs for early syphilis seems unconventional, and would hardly be necessary if the dosage of bismuth had been larger. No particular preference is shown for mapharsen over neoarsphenamine, but it is at least questionable if 0.01 g. of the former is equal to 0.1 g. of the latter in therapeutic effect; in the massive 5-day therapy it took 1.2 g. of mapharsen to produce as good results as 4.5 g. neoarsphenamine. It is of interest to note that for certain types of neurosyphilis Howles favours the Swift-Ellis treatment, one which many regard as *démodé*, and for non-specific protein therapy he gives his typhoid vaccine subcutaneously (p. 453); most people find the intravenous route more effective.

Taken as a whole this book gives an excellent account of the clinical picture, but the treatment recommended will not appeal to everyone; errors and omissions will, it is hoped, be corrected in a future edition. Nowadays, with syphilis so rife, what is wanted is an authoritative guide for the practitioner and one which can be relied upon as correct in every detail.

## AN ATLAS OF HUMAN ANATOMY

*An Atlas of Anatomy.* By J. C. Boileau Grant, M.B., Ch.B., F.R.C.S.Ed. In two volumes. Vol. I: Upper limb, abdomen, perineum, pelvis, lower limb; Vol. II: Vertebrae and vertebral column, thorax, head and neck. (Pp. 390; illustrated. 55s. set of two volumes.) London: Baillière, Tindall and Cox. 1943.

This work in two volumes, and comprising a large number of original plates, has been produced by J. C. Boileau Grant, professor of anatomy in the University of Toronto, who, with the co-operation of a fine staff of dissectors, photographers, and artists, has provided an excellent pictorial record of human anatomy, which will be of great value to students, teachers, and practitioners, and will serve as a sure guide towards the acquisition of a clear mental picture of the chief anatomical features of the human body. Special methods have been employed for the sake of accuracy; these have involved the use of photographic films, and the making of tracings and enlargements of these, which have served as a basis for the "line" and "half-tone" drawings. Moreover, in many of the plates colours have been introduced, all important parts have been clearly labelled, and special observations noted in the form of captions.

Where many have taken part in the production of a composite work it is difficult to pick out anyone for particular commendation, but we would like to draw attention to the excellent half-tone drawings of Mrs. D. Chubb as being specially worthy of mention and as imparting a high artistic character to the work as a whole. The method which has been adopted of a uniform representation of parts drawn from the right half of the body only, so that successive figures may be easily compared, has the advantage which is claimed for it by the author. In practice, however, the surgeon has to deal with the left side as often as with the right, and the effort needed to recognize the change in the relative position of the parts on the two sides of the body is perhaps repaid by the equal familiarity which is gained from a visual knowledge, obtained by the haphazard (or, better, the systematic) study of both the right and left sides of the body. Thus a beginner, when examined on a part belonging to the opposite side of the body to that which he has dissected and fixed his attention on, is often at a loss when confronted for the first time with a "looking-glass transposition" of the parts he is required to identify, and the same difficulty has to be overcome in the study of illustrations which are confined to one side.

Owing to careful revision there are very few errors which have escaped detection, and perhaps only one of these need be noted—namely, in Fig. 346 the adjectives "major" and "minor," with reference to the posterior rectus muscles of the occipital region, have become transposed. The atlas as a whole is thoroughly reliable, and the author and his collaborators may be congratulated on the production of an anatomical work of very high standard and great utility.

## A DOCTOR IN BURMA

*Burma Surgeon.* By Gordon S. Seagrave. (Pp. 159; illustrated. 9s.) London: Victor Gollancz. 1944.

On the cover of this book there are quotations from two American reviews, saying—this is "one of the great stories of the war," and "a book filled with great deeds." Neither of these is an overstatement.

Dr. Seagrave was born and bred in Lower Burma and went to America for his medical education. While at Johns Hopkins he decided to become a medical missionary. He was of a very practical and resourceful nature, and one day, before he left the hospital, he noticed the operation-room attendant throwing away a basketful of broken-down surgical instruments, beyond repair. He asked if he might be given these castaways, and, as he says, "With them all my surgical work in Burma was done, for five years, in spite of the fact that they were broken and not mates—many of the haemostats would not remain clamped but would spring apart and permit large haemorrhages in the most embarrassing part of the operation." On arriving in Burma he was ordered to Nankham in Southern Burma. With his wife to help him he decided to build a hospital there, and with the aid of an old broken theodolite to survey the site of the hospital, which was to be built on a hill top, and the help of a missionary from Moulmein, and no previous experience in house construction, he produced his 100-bed hospital. As soon as the building was finished it filled up rapidly, and continued to run to capacity. He says the most common diseases in the Shan States are, in sequence: malaria, goitre, amoebic dysentery, gonorrhoea, and syphilis. He trained a staff of Burmese girls as nurses, and developed a large jungle practice, performing many major surgical operations.

The first half of the book is the story of an independent, self-reliant, and successful missionary doctor. Then came the war—the Battle of Burma—into which, with his staff of nurses and his equipment, he threw himself whole-heartedly. The Allied authorities at Rangoon gave him a number of trucks with which to carry on his medical work among the British, American, and Chinese troops in their retreat before the Japanese invasion. Then ensued months of peril and extreme hardship for them all. His loyal Burmese nurses were splendid all through. The cheery optimism of Dr. Seagrave was a constant encouragement to everyone. That his work was much appreciated is shown by the fact that he was promoted to the rank of lieut.-colonel and awarded the Military Cross.

This book tells of almost incredible "deeds of derring-do," written in a modest matter-of-fact way. It contains much information about conditions in peace and war, of deep interest to medical men and the general public.

## Notes on Books

It was in 1904 that Sir ROBERT HUTCHISON published in book form his *Lectures on Diseases of Children*, originally given to students of the London Hospital; and those of us whose memories go back 40 years can well recall their eager first reading of this introduction to a subject which they knew to be important but which was sadly neglected in most general teaching hospitals. The book went through seven editions and eleven reprints in 32 years as the single-handed work of its author. For the eighth edition (1941) he entrusted the duty of revision to Dr. ALAN MONCRIEFF, who is responsible also for the ninth (Edward Arnold; 21s.). There was out-of-date matter to be pruned away and new work waiting to be grafted in. Dr. Moncrieff has handled the task with discretion and piety, leaving as much as possible of the original text while bringing it into line with recent advances in diagnosis and treatment. The principal changes are indicated in his preface. The result does him credit and assures this famous book a further period of useful life.

*Treatment by Manipulation* (H. K. Lewis and Co.; 16s.) is the fourth edition of Mr. A. G. TIMBRELL FISHER's book originally published in 1925 under the title *Mahipulative Surgery*. Notwithstanding the short interval since the third edition many changes have been made and some sections largely rewritten in the light of further experience and as the result of helpful criticisms; there are also a number of new illustrations of manipulative technique. In time of war manipulation acquires added importance because it so often enables disabled Service men or women, or the factory worker, to return to duty in the shortest possible time. It will also play a most important part in the treatment of many orthopaedic disabilities which, in spite of the great advances in treatment of wounds and injuries, will become a heavy charge upon the nation after the war.

"An international institution like the Red Cross at Geneva may receive from abroad an urgent request for antityphus vaccine and may hesitate whether to send the vaccine employed against enteric or that used against typhus fever." Typhoid fever has the Latin equivalent "typhus abdominalis," often shortened to "typhus" in Germany and some other countries. Because of such confusion in nomenclature the Joint Relief Committee of the International Red Cross asked at the end of 1942 for lists of terms denoting the various communicable diseases in different European languages, and Dr. YVES BIRAUD, whose experience in connexion with the League of Nations and the International Conference for the fifth revision of the Causes of Death fitted him admirably for the task, has prepared a *Polyglot Glossary of Communicable Diseases* to meet this need. After an introduction and an explanatory section, the disease names included in each successive international number 1 to 44 (infective and parasitic diseases), and communicable diseases occurring in other parts of the International List, are set out in columns comprising the 24 principal European languages, including Russian, Turkish, and Icelandic. Slav languages, using symbols derived from the Cyrillic alphabet, have been transposed phonetically (according to French pronunciation) into Latin characters, as indicated in a table. Many who use the *Glossary* will be grateful for this transliteration. An alphabetical index follows, referring each name to the international number in which it will be found and to the appropriate language column. For all who are interested in international medicine this work will be invaluable. It is published in London by Allen and Unwin at 4s.

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## LOCALIZATION IN THE CEREBRUM AND CEREBELLUM

Understanding of the nature of the representation of function in the cerebral cortex was improved in the war of 1914–18 by a study of gunshot wounds in man. This study was mainly based upon careful clinical observation, unaided by the electrical tools which are available to-day. Between the two wars the study of the cortex was greatly helped, as Prof. E. D. Adrian points out in his Abrahams Lecture, printed in last week's *Journal*, by the development of electronics and by the production of barbiturate anaesthetics. The research which these advances have made possible led to a great increase in knowledge of the functions of the cortex of lower animals, and to an application of that knowledge to the understanding of functional representation in man described by Head, Holmes, Foerster, and others.[1] Experiments on man, carried out since by Foerster[2] and by Penfield,[3] were largely confined to observing the results of stimulation of the motor and sensory areas of the cortex, and mapping out the areas of cortex which gave rise to characteristic responses. Animal experiments followed the same course—that of stimulation of small areas of cortex, which were carefully charted, and of observing the resulting peripheral activity, which might be the twitch of a limb, an apparently purposive movement, the response to a sensation, or an electrical discharge in a peripheral effector. An elaboration of this technique led to the long series of important experiments by Dusser de Barenne, who applied strychnine to minute areas of cortex. Before long the brain became mapped into an elaborate mosaic of functional areas, which often seemed to have an encouraging similarity to the cyto-architectonic areas which had been described after histological studies by Brodmann[4] and the Vogts.[5]

About a decade ago a most important change in experimental method occurred. People began to observe what happened in the cortex when peripheral end organs were stimulated. This was the result, of course, of the phenomenal development of thermionic-valve amplifiers, which were not available to earlier workers. It was encouraged, too, by the observation of the slow electrical changes which can so easily be recorded from the cortex, and which go to make up the electro-encephalogram. In 1933 Gerard, Marshall, and Saul[6] found that displacement of a few hairs on the body surface caused a minute and sharply localized electrical change in the opposite cerebral hemisphere. They pursued this observation and made a systematic study of the cortical changes which resulted from tiny stimuli in different parts of the body. The full results of observation of the cortical electrical potentials caused by lightly touching different parts of the monkey were published by Woolsey, Marshall, and Bard[7] in 1942. In this paper they gave detailed maps of the cortical representation of touch. At the same time as this work was taking place in America Adrian was engaged in a similar investigation over here.[8] He, also, found it possible to map out with great accuracy the cortical points where electrical potentials arose when different areas of skin were lightly stimulated. He drew up charts of the representation of touch in different animals. Some of the species differences are fascinating and throw light upon the way that the cortex deals with skin sensation. For instance, Adrian found that in the goat and the sheep most of the sensory cortex is concerned with messages received from the lips, the feet having a small cortical area, and the body hardly any at all, while the pig's snout has an enormous representation, area for area greater than that of the human hand, although the pig's body has no evident cortical representation at all. At the same time the spatial relationship of the cortical points subserving different areas of the body surface is constant, and, as Woolsey, Marshall, and Bard showed, is in general outline similar to that described from observation of human subjects. Nevertheless, although the excitable areas can be mapped with such accuracy, the representation of touch is as much functional as anatomical, since those areas of skin having the greatest application to the animal's mode of life had the greatest corresponding areas in the cortex.

The cortical representation of sensation does not take the form of an immutable, flat mosaic, where each nerve cell receives impulses from a single receptor or group of receptors. There is overlap between the skin areas represented, and there is electrical evidence of variations in the degree of response of single points from time to time. There is in fact the same kind of functional representation in the sensory cortex as Walshe[9] has urged for the motor—a vital process of representation, in which the behaviour of each point is modified by its near or distant neighbouring points according to the demands of the moment. Bard and his colleagues have shown that, although the dermatomes of the body can be charted in the sensory cortex by means of the electrical discharges which result from stimulation, they overlap greatly, rather in the same way as the tiles of a house. Although stimulation of a given area of skin may evoke with great readiness a response from a fixed and minute area of cortex, it can also evoke responses from a wider area. Both function and structure are represented together, for they are inseparable; but the anatomical representation is based not on the size but on the relative functional values of the skin areas concerned—or, in other words, on their innervation density. Similar investigations have been made upon the excitable cortex which subserves vision (Bartley and

1 Head, H., *Studies in Neurology*, 1920, London.
2 *Lancet*, 1931, **2**, 309.
3 Penfield, W. G., and Boldrey, E., *Brain*, 1937, **60**, 389.
4 *Vergleichende Lokalisationslehre der Grosshirnrinde*, Leipzig, 1909.
5 *J. Psychol. Neurol.*, Leipzig, 1919, **25**, 279.
6 *Proc. Soc. exp. Biol.*, N.Y., 1933, **30**, 1123.
7 *Johns Hopk. Hosp. Bull.*, 1942, **70**, 399.
8 *J. Physiol.*, 1941, **100**, 159; *Brain*, 1943, **66**, 89; *Lancet*, 1943, **2**, 33; *J. Neurophysiol.*, 1943, **6**, 289.
9 *Brain*, 1942, **65**, 409.

Bishop[10]; Talbot and Marshall[11]) and hearing (Bremer[12]; Galambos and Davis[13]), and, in general, similar results have been obtained, for specific stimuli cause nerve discharges in characteristically arranged points in the cortex. A sound of a given pitch affects one fibre; but if its intensity is increased it will affect another, and when the impulse, which is an ordinary nerve discharge, reaches the appropriate points in the cortex it gives rise to an electrical discharge which looks the same as those in the visual or somatic sensory areas. How the association areas of the brain change these similar impulses into different modes of sensation is another problem altogether. Prof. Adrian's fundamental work on the electrical activity and representation of function in the cortex of the cerebrum and cerebellum is rapidly falling into line with similar work from several laboratories in America, some of which has been quoted: It is forming a basis for such a great advance in knowledge that, in his own words, "it is difficult to foresee how far it may not go."

## EPIDEMIOLOGY AND EVACUATION

After the outbreak of war large numbers of children were evacuated from areas exposed to bombing; although many returned within a few months there was another outward movement when, in 1940–1, bombing began on a large scale. From May, 1941, until 1944 the danger was not acute in the great cities; it has only become so since flying bombs began to be launched, and mainly affects London and other built-up areas in the south of England. The scale of the new exodus is large, and it is of interest to summarize the epidemiological results of the earlier movement. On general principles it was to be expected that the movement of town children into the country or smaller towns, associated as it was with the complete or partial closure of schools in the target area, would lower the incidence of the infectious diseases of children in the target areas and raise the incidence upon children in the reception areas. To test this hypothesis required a mass of detailed information not accessible to private students, but fortunately Dr. Percy Stocks of the General Register Office was permitted to publish in the *Journal of the Royal Statistical Society*[14] two papers giving a complete view of the facts; these papers, supplemented to some extent by contributions to the discussions from various experts, are the most important contribution to pure epidemiology in England and Wales the war has produced. It may be said at once that expectation was justified. To take a single illustration: in the administrative county of London the incidence rate of diphtheria in the fourth quarter of 1939 was a third less than that of the second quarter; in great towns which were reception areas the estimated increase of the incidence rate varied from a rise of 9% to one of 122%, with an average of 73%. A point of interest was that, if reception areas were classified by the ratio of immigrant children to resident children, the increased incidence on the latter did not increase *pari passu* with the ratio. A possible explanation, partly supported by evidence given in the discussion, would be that the intimacy of commingling of the visiting and resident children did not increase as the number of the former; for example, there might be separate use of schools when the numbers justified this. One has a parallel in experimental epidemiology in which the problem was studied, as it were, in reverse, susceptibles being added to an infective population. It was found that regular small accessions had on the whole a greater effect in keeping up mortality than sudden large accessions.

What was true of diphtheria and scarlet fever was, in a general way, true of measles and whooping-cough. In measles there was evidence that epidemics which had been expected in evacuation areas were delayed; the epidemic expected in London was three or four quarters late, and there was a lesser delay in Liverpool, Sheffield, and Manchester. In view of the fact that in New York an expected epidemic in 1940 was also three quarters late, although there was no evacuation, there was some discussion whether the obvious explanation—viz., that a reduction in the proportion of susceptibles in the population had broken the periodicity—could be accepted, and the hypothesis of Brownlee which gave weight to a possible mutation of the *materies morbi* was canvassed. On the whole speakers favoured the view that evacuation was the prime cause, and that school closure in the target areas was an important link in the chain of factors making for reduction of means of transferring infection. During the months of heavy night bombing there was great congestion in some places of safety, but the unfavourable effect of this was more than offset by the outward movement of juvenile population.

We have mentioned only a few general results. The two papers contain detailed analyses which should be studied and data which enable other students to investigate matters not discussed. Under our new calamity, outward movement began approximately a month sooner than in 1939; how long it will continue and its ultimate volume are not within our powers of reasonable conjecture. Assuming a similarity of conditions, we should, however, expect that the epidemiological results will conform to those of 1939–40.

## THE QUESTIONARY

The answers to the Questionary on the White Paper, prepared at the request of the B.M.A. by the British Institute of Public Opinion, have now been sifted and analysed by the Institute, and the results are published in this week's *Supplement*. No doubt they will be interpreted variously by different people according to their predilections. Clearly there are limitations to this method of inquiry, which, according to a well-known Public Relations Officer, Mr. E. Rawdon Smith, is "rather like taking the patient's temperature and relying only upon that for a diagnosis."[1] But, within its limitations, the analysis affords a guide to trends of opinion within the profession, and within different groups of the profession. Some critics have committed themselves in advance. Prof. Major Greenwood has thrown doubts on the fitness of the Questionary to

[10] *Amer. J. Physiol.*; 1933, **103**, 159.
[11] *Amer. J. Ophthal.*, 1941, **24**, 1255.
[12] *C. r. Soc. Biol.*, Paris, 1938, **130**, 257.
[13] *J. Neurophysiol.*, 1943, **6**, 39.
[14] *J. roy. Statistical Soc.*, 1941, **104**, 311; 1942, **105**, 259.

[1] *Supplement* to the *British Medical Journal*, July 29, p. 21.

obtain objective answers to questions on the White Paper, stating: "On the assumption that an unbiased opinion given by persons who had read the White Paper was desired, the Questionary is bad."[2] Dr. D. G. Leys and Dr. Horace Joules challenged the validity of the Questionary thus: "Unfortunately the B.M.A., in obtaining the services of the British Institute of Public Opinion, casts a cloak of impartiality over what is in fact a tendentious document. To many doctors some of the questions as put will be unanswerable, since they are framed neither upon general principles nor Government policy, but upon the policy of a section of the profession only, and, moreover, a policy which represents a considerable retreat from the relatively forward-looking programme established by the Planning Commission set up by the B.M.A. itself in 1942."[3] For the most part the Questionary was answered and sent in within a few weeks of publication of the White Paper. The small return of answers from men in the Services is to be noted.

The Questionary was sent to 53,728 medical men and women, and replies have been received from 25,435, this apparently constituting a "world record" for an inquiry of this nature. Answering the general question "Are your reactions to the White Paper favourable?" 53% said "No"; and, although 40% assessed their reactions to the White Paper as favourable, only 32% believed that the introduction of a National Health Service would enhance "the quality of the country's medical service." On what is called the "100% issue," 60% of all groups supported the White Paper proposal that the National Health Service should include everyone: it is worthy of note that 54% of the consultants and 54% of the general practitioners voted in this way. Fifty-five per cent. agreed that the general practitioner should be under contract with a Central Medical Board, and 68% approved the principle of health centres: of the general practitioners 59% approved and 32% disapproved of health centres; but 63% of G.P.s disagreed with the proposal that doctors working from health centres should have a joint contract with the C.M.B. and the local authority owning the health centre. Question 17 asked: "Bearing in mind that 'the doctor practising in a centre will not be debarred from private practice outside it,' what method of remuneration would you like to see adopted for doctors working in health centres?" Twenty-eight per cent. of all answering were for payment by salary; 34% favoured a small basic salary plus capitation fees; 23% voted for payment by capitation fees; and 6% wanted to have capitation fees pooled. For payment in separate practices a still smaller percentage wanted payment by salary, and the majority preferred capitation fee.

Some points of interest arise in the replies to questions on administration. For example, 91% believe that the Central Health Services Council should have the right to publish an annual report, and also the right to publish advice at its own discretion; 76% regard the proposed set-up of the Joint Boards as unsatisfactory, and 80% would like to see doctors and other health workers directly represented on the Joint Boards. The B.M.A.'s Principle D stated: "The profession rejects any proposal for the control of the future medical service by local authorities as at present constituted": 80% of all groups considered that the White Paper infringes this principle. The proposed power of the C.M.B. to prevent doctors starting public practice in an over-doctored area was viewed favourably by 57%; but 66% objected to the power of the C.M.B. "to require the young doctor during the early years of his career to give his full time to the public service where the needs of the service require this." The answers to the question (9a) on central administration showed, according to the B.I.P.O., that many doctors feared that the medical profession would come under political control.

These are just some of the points; for the rest readers should turn to this week's *Supplement*.

[2] *Lancet*, April 1, 1944, p. 451.
[3] Ibid., April 8, 1944, p. 486.

## PENICILLIN PRODUCTION

Until recently penicillin was available in so small an amount as to be for most people a medical curiosity; only a few isolated patients were able to benefit by it. Another series of papers in this week's *Journal* provides further evidence of the tremendous strides made by the pharmaceutical industry, which is now putting penicillin at the disposal of medical men working in widely varying fields. For these supplies we are largely indebted to our American friends, who have won the third victory in the penicillin field. The first was Fleming's discovery; the second was the victory of Florey and his colleagues, who showed how to obtain penicillin in relatively pure form, and who demonstrated its clinical use. There remained a third problem—to produce it on a large scale. It is this problem which the Americans have solved, and we owe much to their foresight, energy, and correct estimation of the magnitude of the effort required. The credit for the supplies of penicillin is chiefly due to Dr. A. N. Richards, the chairman of the Committee for Medical Research, one section of the Office of Emergency Management in which President Roosevelt develops his measures for prosecuting the war. Dr. Richards, formerly professor of pharmacology at the University of Pennsylvania, is well known to workers on renal physiology. He devised the method of withdrawing fluid for examination from the renal tubule. As chairman of the Committee for Medical Research his main concern was with research and not with production, and he might well have taken the view that the question of the supply of penicillin was no affair of his. Nevertheless he seems to have realized, when Florey took the news of his findings to Washington late in 1941, that here was a question on which the pharmaceutical manufacturers required guidance and encouragement. Dr. Richards must have taken a heavy load of responsibility on his shoulders in recommending the enormous outlay on plant necessary to make the present supply of penicillin possible. Yet he took this responsibility in face of the chance that at any moment a synthetic process would render obsolete the plant for growing the mould. The synthesis of penicillin by a method practicable on a large scale has not yet been achieved, and so Dr. Richards has the reward of knowing that as a result of his effort the lives of very many American and British wounded are being saved every day. We can acknowledge this debt to the U.S.A. without in any way disparaging the efforts which have been made to the same end in this country. British manufacturers, although hampered by a far greater shortage of material and labour, furnished most of the penicillin which has been used by Army casualties in the Mediterranean theatre of war, and for research purposes in this country, and are now contributing to available stocks on an increasing scale.

## RESEARCH IN OPHTHALMOLOGY

We announce elsewhere in this issue the decision of the Council of the Royal Eye Hospital to establish an Institute of Ophthalmology—a decision that will, we hope, bear fruit in an advance of knowledge in this important branch of medicine. It is substantially true that medical research

in this country is still very largely a matter of individual effort. Research "foci" rather than research "centres" have tended to develop. By good fortune it has happened that occasionally a tradition for research has centred at a particular hospital for more than one generation, but more often the passing of an outstanding figure has also meant the decline of the particular focus from prominence. In recent articles in this *Journal* stress has been laid upon the man rather than the organization. This thesis was eloquently stated by Dr. F. M. R. Walshe,[1] and has been elaborated in relation to ophthalmology by Sir John Parsons.[2] Dr. C. G. Kay Sharp,[3] pointing out that "planning for research" and "planning of research" are not synonymous, has stressed the need for organized facilities through which the individual worker can express himself. The distinction made by Dr. Kay Sharp is not unimportant, and it is mainly owing to his initiative that the planning for ophthalmic research has become a reality. Some six years ago in a letter in these columns[4] he stressed the need for national planning in the prevention of eye disease, and advocated that in the first place the local authorities, who jointly spend over £2,000,000 annually for the welfare of the blind, should set aside 1% of this expenditure to establish a central research fund, and, secondly, that some four research centres be set up in closest co-operation with existing ophthalmic centres—one in the North of England, one in the Midlands, and two in London.

It is gratifying to record that a move in this direction is now being made. The County Councils Association and the Association of Municipal Corporations have agreed, on the recommendation of their Joint Blind Welfare Committee, that a sum at present estimated at about £20,000 ought to be provided annually by the county and county borough councils to subsidize planned and co-ordinated research. The associations also foresee the establishment of a National Ophthalmic Research Council to administer the proposed funds, and it is contemplated that in the first instance five research centres should receive subsidies according to their need. This scheme is to be submitted to the Ministry of Health, and, later, the necessary concurrence of the individual county and county borough councils will be sought. Two research centres have come into existence since Dr. Kay Sharp's letter of 1938—one at Oxford and the other the research unit at the Royal Eye Hospital. The pioneer efforts of both these centres amply justify support.

## MALARIA CONTROL IN NORTH-EASTERN INDIA

The report of the Committee of Control of the Indian Branch of the Ross Institute of Tropical Hygiene for the year ending July 31, 1942, was reviewed some little time ago in this *Journal*. Regarding the general tenor of the report for 1943 little need be added to what was said in our review of its predecessor. But one important feature should be mentioned—viz., that with the report for 1943 is incorporated a summary of the principles underlying malaria control in India, with special reference to the North-Eastern Frontier. This was drawn up by Dr. G. C. Ramsay and incorporated in the report to meet requests by several military medical officers for copies of Dr. Ramsay's publications. Since Dr. Ramsay's experience of antimalaria work in North-Eastern India must be unique, this brief but excellently condensed conspectus of possible methods of malaria control has additional interest now that the part of India to which it refers has come so prominently into the war picture. Starting with a brief account of the breeding-places of *A. minimus*, the chief carrier in North-East India, Dr. Ramsay deals seriatim with stream training, oiling, paris green, cuprous cyanide as a larvicide, water pollution as an antilarval measure, and control of breeding in kutcha wells. These are all classed as temporary measures. The permanent measures, which should replace temporary ones whenever possible, are site selection, provision or preservation of dense shade over water channels, flushing, drainage, flooding, subsoil methods, fascine drainage, concrete inverts, vertical drainage, flooding, control of irrigation, filling, and zooprophylaxis. Notes on *A. sundaicus* and *A. philippinensis*, which are important under certain conditions, and on biological methods are also added. Under these heads are given in a few words the relevant and salient points about each; altogether an excellently informed review of measures adapted to this region of India. In appendices to the report the long list of firms and other subscribers to the Indian Branch testifies to the success of this co-operative scheme for improvement of health on estates and other labour-employing concerns which has been initiated and ably carried out under the Ross Institute.

## MINERS' DISEASES IN THE PAST

Thousands of years ago men were delving into the earth to find the raw materials on which ancient civilization depended for its existence. After the stage of primitive surface mining had passed, underground mining produced a surplus of materials which exceeded the needs of the few who owned the mines. So mines became a source of great wealth, while the miners, who were slaves or prisoners or criminals sent underground to expiate crime, toiled in the stifling stench and produced the wealth desired by society. The almost complete disregard of the miner and his diseases by ancient medical authors expresses the social indifference to the industrial worker of those times. Later studies by physicians of the Middle Ages, particularly Agricola and Paracelsus, and the periods which followed up to the end of the nineteenth century showed the increasing interest taken by the medical profession in industrial diseases. But while physicians proposed various preventive measures they were in no position to make them effective. Any improvements made in mining conditions came as a result of technical advances in engineering and of Acts of Parliament, which were the products of public opinion and nineteenth-century trade unionism rather than the fruits of medical research. These Acts were designed primarily to prevent the catastrophic explosions which inflicted great loss of life and the exploitation of women and children underground. Nevertheless they did exert a salutary effect on the health of mine workers. In his recent monograph[1] Dr. George Rosen has given a historical analysis of one industry which shows clearly the factors that retard or accelerate the development of an industrial society. Those who are interested in the application of medical science to social problems should read it, because from the past there are lessons to be learnt for the future. It is probably the first document of its kind to show so clearly that the prevention of disease among workpeople must be the collective responsibility of society, and that our profession acting alone can achieve very little even with special knowledge of the relation between work and health. The author finishes his story at the end of the nineteenth century. May he fulfil his hope to tell the more recent history of diseases among miners in a companion work.

[1] *British Medical Journal*, 1944, **1**, 173.
[2] Ibid., 1944, **1**, 430.
[3] Ibid., 1944, **1**, 697.
[4] Ibid., 1938, **2**, 594.

[1] *The History of Miners' Diseases. A Medical and Social Interpretation.* By George Rosen, M.D. With an introduction by Henry E. Sigerist, M.D. New York: Schuman's. ($8.50.)

# REGISTRATION OF SPECIALISTS

## THE G.M.C. ASKS FOR LEGISLATION

The General Medical Council, sitting *in camera* at its recent May session, approved a report with recommendations from a special committee which has been considering the registration of specialists. This committee, under the chairmanship of Prof. Sydney Smith, and with Dr. H. Guy Dain as one of its members, was appointed in November, 1943, to report on the steps which should be taken by the Council concerning the admission of specialists to a statutory register. It was asked to consider the conditions of admission both during and after an interim period, the conditions under which postgraduate qualifications might be held to deserve recognition, and the postgraduate experience which might be regarded as enabling a practitioner to be registered as a specialist.

### The History of the Matter

Proposals for a register of specialists had already been made. One such appears in the draft interim report of the Medical Planning Commission, which calls for an authoritative committee to determine the standards conferring consultant status. The White Paper spoke of the need for more consultants and a better distribution of them, adding that one of the aims of the proposed National Health Service would be to encourage more doctors of the right type to enter this branch of medicine or surgery and to provide the means for their training. The White Paper, however, stopped short of proposing in detail a form of consultant service,[1] and stated that the Government was awaiting the report of Sir William Goodenough's Committee on Medical Schools. That report was published a fortnight ago (*Journal*, July 22, p. 121).

In the House of Commons in February last the Minister of Health announced that local lists of practitioners who fulfilled certain conditions of admission to a specialists' register were being compiled by Area Committees under the supervision of the Central Medical Academic Council. This Council is a body set up by the Royal College of Physicians of London, the Royal College of Surgeons of England, and the Royal College of Obstetricians and Gynaecologists, and in addition to representatives of the Colleges includes representatives of the British Medical Association and of the eleven universities in England and Wales which are licensing bodies. The Area Committees cover England and Wales in eleven regions, of each of which a university is the centre, and the membership includes the vice-chancellor, the dean of the faculty of medicine, and representatives of consultants and general practitioners. Local lists in Scotland have also been compiled, but by a different method.

The criterion for inclusion in the specialists' list during the interim period, for immediate administration purposes, is that the practitioner has acted as a specialist in the past and is generally recognized as a specialist by other practitioners in the area where he practises. No doubt after the interim period some more closely determined conditions will be laid down for admission, as, for example, training at an approved hospital, a minimum period of experience, the possession of a higher degree or diploma, the holding of a recognized appointment, and an undertaking not to engage in general practice. The General Medical Council committee, however, has not yet determined what it calls the "future consultant (or specialist) status," and has so far dealt only with the interim status. In February last, while its committee was still engaged on this work, the Council reaffirmed its view that in the public interest it was desirable that a statutory register of specialists should be formed and maintained by the Council and that the conditions of admission to such a register during the interim period should be those just stated—namely, that the practitioner had acted as a specialist and was recognized as such by other practitioners in his area.

The immediate or interim purpose of such a register of specialists would be to provide the Government and the municipal and participating voluntary hospitals—i.e., the authorities responsible for organizing a service of specialists as part of the National Health Service—with an authoritative and convenient means of ascertaining whether a particular practitioner is eligible to hold such an appointment. It follows that the register must be available at a date not later than that on which a service of specialists may be inaugurated as part of the National Health Service outlined in the White Paper.

On the recommendation, therefore, of its special committee the General Medical Council has resolved to represent forthwith to the Privy Council that legislation be introduced empowering the Council to make and maintain a register of specialists, such register to be available not later than the date of commencement of the service.

### The Form of the Register

The next question to which the committee of the G.M.C. addressed itself was the form which such a register should take. Should it be a book separate from the *Medical Register*, or an appended list forming part of the *Medical Register* itself; or should there be a separate column in the *Medical Register* to denote a specialist, or use be made of the fourth column—the one headed "Qualifications"—for this purpose? All these methods have their advantages and disadvantages. One disadvantage of a separate book—although, to be sure, it applies in some degree to the other methods, for the *Medical Register* is in many public libraries—is that it would be accessible to lay people who believed themselves competent to choose specialists.

In the end the committee decided that the procedure should be to insert the word "Specialty" or "Specialties" opposite the name of the practitioner in the column headed "Qualifications" in the existing *Medical Register*, and to add the subject or subjects in which he had been recognized by the Council as a specialist, with the year of his recognition. Further, for facility of reference, it was decided that the *Medical Register* should contain an alphabetical list of specialties with, underneath each heading, the registered names of the recognized practitioners, again given alphabetically. From this it would be possible to refer to the full particulars of the practitioner given in the main body of the *Medical Register*.

When the Minister of Health, as mentioned above, informed the House of Commons that local lists were being compiled, he made a clear distinction between the restrictions to be placed on the use of the local lists so long as provision is not made by legislation for the establishment of a register of specialists and the freedom of Parliament to determine the manner in which a statutory register should eventually be set up. His words are worthy of quotation:

> "I am, therefore, glad of this opportunity of assuring the profession, and especially its members who are on war service at home or abroad, that such lists will be treated as strictly confidential and will not be used as a test of eligibility for appointment as consultant or specialist in any comprehensive post-war hospital service. If, at a later date, it were thought desirable that consultant and specialist appointments should be restricted to persons qualified in some particular manner and enrolled on a list for the purpose, it would be necessary to provide for the establishment of a register on a statutory basis in a manner approved by Parliament."

The sense of the General Medical Council's discussions on this point is that it is neither necessary nor desirable for the Council to repeat or to revise the work of the Central Medical Academic Council (set up by the Royal Colleges) or of its Area Committees in preparing the local lists for England and Wales, and no doubt the same view would be taken concerning the local lists in Scotland. It is assumed that these local lists are based upon the knowledge of competent authorities of the subject or subjects in which each registered medical practitioner included in the lists is accepted as a specialist.

The recommendation of the committee, accepted by the G.M.C., is that the legislation to empower the Council to form and maintain a register should confer the right of admission to the register upon (1) practitioners on war service abroad whose names are included in any list of specialists, compiled before an appointed day, which appears to the Council to deserve recognition in the register, and (2) practitioners whose names are included in any such list on the ground that they

[1] In the White Paper the terms "consultant" and "specialist" are used as alternatives or as complementary to each other. In the General Medical Council report the word "specialist" is generally used.

have acted as specialists in the past and are generally recognized as such by other practitioners in their areas. The same legislation should confer the right upon any other practitioner to make an application for admission, and should empower the G.M.C. to make regulations prescribing the way in which applications are to be made and determined.

### Future Registration

When, therefore, the service of specialists comes into operation the Government and the hospitals will have available an interim statutory register, first in the form of a series of entries in the *Medical Register* indicating that the practitioners have been recognized by the General Medical Council as specialists in a stated subject or subjects, and also a separate list of specialties with the names of practitioners following. This, however, leaves much to be considered. In the view of the committee the object of a statutory register of specialists kept by the G.M.C. would be to establish and maintain a standard of postgraduate medical qualification and experience such as would guarantee that practitioners who had attained that standard could properly be recognized in the register as specialists. Many, of course, by any standard will be recognized as possessing consultant (or specialist) status, which is valid not only for the interim but for the future period. But questions of some difficulty will arise. It is generally agreed, for example, that specialist status should in future imply the possession not only of postgraduate qualifications but of postgraduate experience; but are such qualifications to be regarded as indispensable for the practice of all registrable specialties, and, so far as they are indispensable, what is the value in relation to specialist status of postgraduate qualifications in medicine, surgery, and midwifery and the postgraduate qualifications in specialties now granted by the licensing bodies? What should be the nature and the duration of the postgraduate experience demanded in each registrable specialty? How far should the powers of the Council to register postgraduate qualifications be extended by legislation?[2] Should provision be made for the Council to consult appropriate professional bodies about the conditions of admission to the register after its initial formation?

This G.M.C. report was issued before the Goodenough Committee's report appeared, and it is expected that the further work of the G.M.C. committee will be much facilitated by perusal of the Goodenough report, especially the section on postgraduate training and experience for intending specialists. It is intended to make a further report to the Council in the light of the Goodenough recommendations as soon as possible.

## BEIT MEMORIAL FELLOWSHIPS

The Trustees of the Beit Memorial Fellowships for Medical Research in their annual report for the year 1943–4 state that they accepted with great regret the resignation of Prof. T. R. Elliott, F.R.S., who had been secretary to the advisory board since 1930, and whose experience and wisdom had been of inestimable value. His place on the board had been taken by Sir Thomas Lewis, M.D., F.R.S., and Dr. A. N. Drury, F.R.S., had been appointed acting secretary.

The following elections were made, with permission for each Fellow to be seconded at any time for war duties:

*Fourth-year Fellowships* (£500 a year).—W. Holmes, M.A., D.Phil.: to continue the study of the regeneration of nerve fibres after injury; at the Department of Zoology and Comparative Anatomy, University Museum, Oxford. Mary F. Lockett, M.D., M.R.C.P.: to continue the study of renal pressor substances responsible for experimental high blood pressure; at the Pharmacology Laboratory, Cambridge.

*Junior Fellowships* (£400 a year).—J. C. Boursnell, Ph.D.: to study the fate and functions of trace and some other elements in the animal body, using radio-active isotopes; at the Department of Biochemistry and Chemistry, the Medical College of St. Bartholomew's Hospital. G. A. Levvy, Ph.D., D.Sc.: to study the adaptive enzymes in the animal body, with special reference to the role of glucuronidase in the metabolism of steroid hormones and related substances; at the Department of Medical Chemistry, University of Edinburgh. H. J. Rogers, Ph.D.: to study the biochemistry of hyaluronidase obtained from various sources, and the role of enzymes such as hyaluronidase and lecithinase and other bacterial antigens in infection; at the Lister Institute, Elstree, Herts. G. J. Romanes, Ph.D., M.B., B.Ch.: to study the relationship between the developing mesoderm and the motor apparatus of the spinal cord supplying it; at the Department of Anatomy, University of Cambridge. F. Sanger, B.A., Ph.D.: to study the chemical structure of proteins, with special reference to insulin; at the Sir William Dunn Institute of Biochemistry, Cambridge. S. P. V. Sherlock, M.B., Ch.B., M.R.C.P.: to study the hepatic function in disease by biopsy methods; at the Department of Medicine, British Postgraduate Medical School. C. Waymouth, Ph.D.: to study the factors influencing tissue growth *in vitro*; at the Physiology Department, University of Aberdeen. E. C. Webb, B.A.: to study the ultimate mode of action of drugs and poisons in living tissues; at the Sir William Dunn Institute of Biochemistry, Cambridge.

[2] A number of postgraduate qualifications are already registrable in the *Medical Register*, including the M.D. and M.S. or its equivalent of all universities, the higher diplomas in medicine and surgery granted by the licensing corporations, and the diplomas and degrees in public health. Diplomas in branches or subdivisions of medicine and surgery granted by universities or corporations are not registrable.

## SCIENCE FELLOWSHIPS FOR BRITISH UNIVERSITIES

The Directors of Imperial Chemical Industries have offered to provide at nine British universities a total of 80 Fellowships to be held by senior workers in certain branches of science—namely, physics, chemistry, and the sciences dependent thereon, including chemotherapy. The Fellowships will be of the average value of £600 per annum and the scheme will operate for an initial period of seven years. The Directors of I.C.I. have described on broad lines the subjects in which the Fellowships are to be held, but the administration of the scheme rests wholly with the universities and no conditions are attached by the directors to their tenure. The Fellows will be members of the university staffs and will be concerned only with the duties laid upon them by the universities. Their primary work will lie in research, but they will also, it is hoped, take some part in university teaching. Oxford, Cambridge, and London have each been offered 12 Fellowships; Glasgow, Edinburgh, Liverpool, Manchester, and Birmingham, 8 each; and Durham 4. It is hoped that by this policy there will emerge a body of men capable of taking high academic or industrial positions, thereby advancing academic research and industrial research, which in the view of I.C.I. are indivisible and interdependent.

## INSTITUTE FOR RESEARCH AND TEACHING IN OPHTHALMOLOGY

The Council of the Royal Eye Hospital has decided to establish an Institute of Ophthalmology where teaching and research can be carried out systematically and co-ordinated with the work of laboratories and of other ophthalmic and of general hospitals. The Institute, with an independent board of governors, will work under the patronage of the Archbishop of Canterbury, the Archbishop of Westminster, the Very Rev. Cyril Golding-Bird, General Sir Bernard Montgomery, and Sir Philip Henriques; and under the presidency of Admiral Sir Edward Evans. A board of governors is being constituted with Mr. James Cadman as treasurer and chairman of the Finance Committee. To ensure that the Institute is broadly based, panels of advisers have been set up to help in the planning and carrying out of the work.

# Reports of Societies

## PNEUMOPERITONEUM

At a meeting of the Section of Medicine of the Royal Academy of Medicine in Ireland in May, with the president, Dr. P. T. O'FARRELL, in the chair, Dr. M. I. DRURY showed one of a series of cases of pulmonary tuberculosis treated by artificial pneumoperitoneum. The patient, 32 years old, had bilateral pulmonary tuberculosis, maximal on the right side, when admitted to Rialto Hospital in June, 1941. Up to May, 1943, he had been treated by rest in bed, after which date he was given two courses of sanocrysin totalling 4.35 g., with continuation of strict bed-rest. In February, 1944, right phrenic crush, done by Mr. T. C. J. O'Connell, caused elevation of the right dome of the diaphragm by 1½ in. Pneumoperitoneum induced shortly afterwards raised this cupola by a further 2 in., as well as raising the left cupola 1½ in. The patient's general condition had improved; sputum had fallen from 4 to 1½ oz. a day; blood sedimentation rate was almost normal; and once for the first time in three years his sputum had been negative for tubercle bacilli. Dr. Drury also showed *x*-ray films of a case of bilateral pulmonary tuberculosis in which both hemidiaphragms were raised by 2½ in. by artificial pneumoperitoneum, although no phrenic interruption had been carried out. Dr. E. T. FREEMAN considered the indication for pneumoperitoneum was adhesions between the lung and the diaphragm.

# Correspondence

## Air Disinfection

SIR,—The paper by Prof. Mudd of the University of Pennsylvania and your leader on the subject of air disinfection (July 15, pp. 67 and 82) contain much of interest to us, but in the section dealing with the progress made in the use of germicidal aerosols there are notable omissions of relatively early work. Portslade laboratories has been occupied almost exclusively with the study of this question since 1937, but it would appear that many observations emanating from other laboratories as well as our own are comparatively unknown.

Rightly or wrongly we have been in the habit of considering Bechhold (1935) as the originator of the aerosol theory, although he did not, to our knowledge, coin the word "aerosol." "Exhaustive experiments unexpectedly show that the action is not caused by gaseous state, but principally by the action of finely distributed material as mist or smoke."

For some 40 years Trillat has been publishing results of his work on the behaviour of air-borne bacteria in various environmental conditions. These studies culminated in his infecting animals with air-borne influenza virus and various bacteria, and preventing infection by means of atomized germicides (1939). We came to the same conclusion as Trillat, a conclusion expressed in Bechhold's own words: "Exceptional effects may be obtained with extremely small quantities, mainly due to their low vapour pressure, the vapour concentration being insufficient to act."

Investigations during the last few years by others and ourselves have led us to conclude that we were wrong in viewing the action of lowly volatile substances as being substantially due to direct contact of the germicide and bacterial particle—a view which was always unacceptable on mathematical grounds to our colleagues Finn and Powell, unless accessory factors were involved. We accept, provisionally, the vapour theory as an explanation for the mechanism of action of lowly as well as highly volatile germicides. It was assumed, and subsequently demonstrated experimentally in the early days of our work, that the latter acted in the vapour phase, being, of necessity, non-existent as mists unless used in amounts sufficient to saturate.

It may be pointed out that considerable work has been done by Trillat, and at Portslade (1940a), on the action of hypochlorites on *salivary* organisms, and the great importance of relative humidity on the activity of these and other types of germicides formed for us a special study (1941). Trillat also has for years consistently emphasized the relative insusceptibility to aerial germicides of desiccated bacteria, which, however, he considered of less danger than those freshly emitted from an infected individual. Again, the observation that propylene glycol is active on air-borne bacteria was, to the best of our knowledge, first made in these laboratories (1940b) and not in America. We felt, however, at the time, that the amount required in order to attain the arbitrary standard of kill we had set ourselves was likely to be prohibitive. The glycol was found to have an activity of the order of ordinary phenol, and this, in the main, has been confirmed in several excellent papers by Robertson and his colleagues.

As regards vapour pressure in relation to bactericidal activity, propylene, diethylene, and probably the other glycols, in our experience, fall into line with the phenols (1944). The results are superior with the highly volatile if the percentage saturation be high, but with the lowly volatile if the percentage saturation be low. At intermediate degrees of saturation results tend to be similar—i.e., an equal bactericidal activity when the amount of germicide atomized is proportional to the amount required to saturate at 20° C. (our working temperature). For instance, as regards the amount of propylene glycol and hexyl resorcinol required to saturate, the ratio is about 500:1, while the proportions in our original mixture were only 9:1. When a large amount of the mixture is used, as was presumably done by Robertson, one would not expect the results obtained with the glycol alone to be improved upon, while when a small amount was used, in our case mostly 10 mg./m.³, the presence of H.R. made a negative result into a strong positive. Even in the latter example there is more than sufficient H.R. to saturate, but only about 1/40th that of the glycol—too low a degree of saturation of any glycol or phenol tested here to give an appreciable kill of salivary organisms.

Thus it appears that, as in the test-tube so in the air, the solubility of the germicide in the medium in which it is operating has an important bearing on bactericidal capacity. Among 20 phenols tested here no member very soluble in water has a high degree of activity in the test-tube, and no member very soluble in the air has a high activity as an aerosol. A low solubility, however, in either medium does not in every instance correspond to a high bactericidal activity in the particular medium. The possible reasons for this cannot be entered into here; they are both numerous and complex. Among other aspects, molecular potency, rate of generation and decay of the germicide mists and vapours, absorption in relation to adsorption, and the competition of the *living* organism compared with the "dead" surround, etc., for the germicide are, perhaps, not the least important.

The concluding remarks in your leader prompt us to state that certainly, so far as we are concerned, disinfection with avoidance of sterilization has been and is the main objective, and we believe that the same applies to most workers in this field. Furthermore, our ideal is attenuation and not killing of the pathogenic organisms. Already Trillat (1932) had shown that vaccination of his experimental animals could be accomplished by inhalation of organisms treated with germicidal aerosols. In connexion with proposed therapeutic or prophylactic measures, the wise advocator never neglects the fundamental biological law that the depriving of an organ of facilities for performing its natural function may ultimately lead to its inability to perform this function efficiently when occasion arises for it to do so.

It remains for future experiments to show whether attenuation will be attained more satisfactorily by utilizing suitable amounts of a slow "killer" (H.R.) than by utilizing a fast "killer" (P. glycol).—We are, etc.,

C. C. TWORT.
A. H. BAKER.
L. J. WHITE.

Portslade Research Laboratories.

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## Fulminating Diphtheria

SIR,—Under this heading (July 15, p. 78) Dr. Strong records a fatal case of hypertoxic diphtheria in a fully inoculated child. Although the combination of factors in this case was unusual, similar cases of hypertoxic or malignant diphtheria are unfortunately not rare in areas which are heavily infected by *C. diphtheriae gravis*. It is not yet generally realized that this organism may sometimes elaborate a lethal dose of toxin within a matter of hours after the onset of symptoms, and that because of this a fatal issue may occur in spite of antitoxin therapy at an apparently early clinical stage.

The presence of "bull neck" with tonsillar enlargement and nasal discharge suggests that the patient suffered a severe nasopharyngeal attack. The fauces then would also show the peculiar translucent oedema which precedes the formation of membrane and which is often accompanied by post-nasal obstruction. Fetor oris and absence of pain are also usual. In Gateshead, after eight years' experience of this type of invasive diphtheria in epidemic form, the presence of "bull neck" is regarded as an indication for massive dosage of antitoxin by the quickest possible route. Even so, doses of 100,000 units given on the second day of the illness have not always saved the patients. In these cases, too, further spread of membrane may be observed over a day or two after treatment by antitoxin, and the subsequent disintegration of the membrane takes a period of a week or even longer. In Dr. Strong's abbreviated clinical report there is no indication of a spread of membrane to the larynx, and one wonders if tracheotomy was performed for that reason.

Surely the nasal contact carrier, who had recovered from a previous attack of diphtheria and was harmless for six months, must be acquitted of the charge of originating the disease. The swab results quoted do not include visitors, whom I would impugn as being much more likely to introduce the organisms, not only to the two cases, but also to the nasal carrier. In these days diphtheria patients are retained in isolation until successive "freedom" swabs have been obtained, and chronic nasal carriers are rare.

Even with fully inoculated patients, clinical phenomena should be the guide to therapy, for there are some individuals unable to maintain immunity against the gravis strains of diphtheria bacilli. If there is relatively painless oedema of the fauces and neck glands with the presence of membrane, large doses of diphtheria antitoxin should be given at once.—I am, etc.,

JAMES GRANT,
Medical Officer of Health. Gateshead.

## The Surgeon and the Anaesthetic

SIR,—I have followed with great interest the discussion on anaesthesia and anaesthetics which has followed the letter from Dr. Elam (Feb. 19, p. 263) on the advisability of publication of all deaths under anaesthesia, which at present are far too high. He says: ". . . it does not at present seem that a noticeable drift away from inhalation anaesthesia and the adoption of other methods are leading to improved results; rather the reverse. . . . A false sense of security will arise, and 'modern anaesthesia' will become (if it has not already done so) far more dangerous than chloroform anaesthesia at its worst." A letter from Dr. Parry Price in the same issue takes the ultra-modern view of many of the younger generation—that chloroform should be entirely discarded in favour of other methods, such as intravenous injection of pentothal.

Chloroform inhalation still has some advocates, especially perhaps among the older generation. There are two reasons why chloroform is less in favour, especially among professional anaesthetists, than ether, gas and oxygen, and intravenous injections of a new and relatively untried drug, such as pentothal. First, there is a widespread idea, which I believe to be entirely without justification, that light chloroform anaesthesia is especially dangerous, and that sudden death from vagus inhibition may accompany even a trivial operation unless the patient is fully under the anaesthetic. This seems to be a tradition handed on by some physiologists who have had no surgical experience, and I am quite sure it is entirely wrong. The first effect of light chloroform anaesthesia is upon lower sensory centres, producing analgesia, before there is any interference with special senses or the slightest mental confusion; in fact, the sense of hearing becomes if anything more acute. The patient can answer questions, and open his mouth while sitting up in bed, and minor operations can be performed, such as tooth extraction, opening a superficial abscess, or removal of a packing in a wound, while the patient knows what is being done but feels no pain, and there is no sign of nausea or disturbance of any kind.

Another reason for the unpopularity of chloroform is that a death during the administration of chloroform is in the vast majority of cases the fault of the anaesthetist and due to an overdose of the anaesthetic narcotizing the respiratory and vasomotor centres in the medulla. It occurs on the operating table, entailing an inquest, while a death from ether, when it does take place, more often occurs later and there is no inquiry.

The surgeon should choose the anaesthetist who will give the anaesthetic he prefers in the manner required and not continue the inhalation unduly. It too often happens that the patient is still deeply under the anaesthetic when the operation is over, and may not recover consciousness for perhaps an hour after returning to the ward. Unless he is carefully watched by an efficient nurse a catastrophe may occur, such as the sudden pulling out of a tube in the intestine draining the bowel, with fatal results. The patient should be recovering consciousness when the operation is nearly over, and be fully conscious when returned to the ward. The post-operative nausea and vomiting will be much less prolonged. Chloroform is more agreeable to the patient than ether even when both are given by an open method; and a comfortable and quiet night before the operation may be obtained by a small injection of morphine and atropine or a drug such as omnopon.

Pentothal, which seems to be so popular at the present time, is by no means free from danger, and the dose cannot be as accurately judged and fitted to the requirement of the operation. When once injected into the blood it cannot be removed until its time is up. In your issue for July 15 (p. 93) there is a letter on pentothal anaesthesia in which the writer claims to have used pentothal extensively since it came on the market, and attributes the fact that he has never yet had a fatality to a very lively respect for this powerful anaesthetic agent. To avoid fatalities he would insist on the following. It should be administered by experienced anaesthetists only; no rank-and-file medical officer should be allowed to use this powerful—dangerous if you like—drug; he gives a list of the cases in which it should never be used if anxiety is to be avoided; the following should always be at hand: oxygen, picrotoxin, ephedrine, and coramine, and the doctor conducting the anaesthetic should know how and when to use them. "Even the most experienced anaesthetist," he writes, "exercising the greatest care and vigilance, will get when he least expects it a reminder that pentothal anaesthesia is not always 'child's play.'" What an extraordinary advertisement from an ardent "fan." However, he used it to extract four teeth! Surely a whiff of the despised chloroform would be quite sufficient, as I have proved on many occasions, and *quite free from any danger*.—I am, etc.,

Worthing. HERBERT H. BROWN.

## Chloroform in India

SIR,—In recent correspondence in the *B.M.J.* about the merits and, particularly, the demerits of chloroform a few important points were not mentioned. This agent has long been used in many parts of the world, including outlying small free hospitals in India, where modern expensive gases and apparatus are not yet available.

While fully aware of the dangers of chloroform and the undesirability of its use, certain factors make chloroform less toxic and relatively safer in a healthy Indian than in a European. This is due to the Indian diet, which is principally carbohydrate and starch, in contrast to the predominantly nitrogenous diet of the West. The population in India is mainly vegetarian. The cereals, pulses and grams, and fruits contain a high percentage of carbohydrates. For instance, the carbohydrate content of the foods in common use is: rice 79%, wheat 74%, maize 66%, bajra 67%, cholam 74%; pulses and grams all above 55%; bananas 36%, plantains 24%, dates 67%, figs 17%, grapes 10%, etc. In addition mangoes, jack-fruits, water-melons, oranges, etc., abound in India; and those concerned in growing sugar-canes and making molasses eat both. Buffaloes' milk and various sweetmeats made of milk and sugar are abundantly taken. The selling of freshly extracted sugar-cane juice and sweetmeats is a common sight in the streets of Indian towns and cities.

Under these dietetic conditions the livers of Indians are well replenished with glycogen, which would hardly be the case with Western people with their almost wholly nitrogenous diet. Sugar tolerance is usually higher in Indians than in Europeans. It has also been recently shown that glucose strengthens the cardiac muscle, and that if an adequate amount of vitamin $B_1$ is taken in the pre-operative diet respiratory enzymes are well produced in the system, and so breathing troubles, other than obstructive, are to some extent prevented. Wheat, pulses, etc., which abound in Northern India, contain vitamin $B_2$; and these and other carbohydrates, and milk products, account for the health and great bodily strength of the people there. Chloroform does not produce any serious hepatotoxic effect in these healthy people, whose livers contain adequate glycogen; also there is hardly any respiratory trouble, owing to sufficient respiratory enzymes—viz., flavo-protein, and coenzymes I and II—from the use of wheat, bajra flour, or maize, and also of toddy, which contains yeast.

From my long experience I am convinced that in strong, healthy, and active Indians living on rich carbohydrate diet the careful use of chloroform merely for inducing anaesthesia produces scarcely any hepatotoxic effect or depression of

respiration and circulation. Any temporary reaction on the liver can be safeguarded by pre-operative use of glucose and post-operative infusions of glucose with insulin.

In certain places where chloroform–ether mixtures were used no serious toxic effects were observed; relaxation was easily obtained and maintained, and no convulsions were seen even in very hot weather. The mixture seems to prevent ether spasms and convulsions, as less ether is needed. Certain medicines containing chloroform are drunk for long periods as carminatives, etc.—e.g., spiritus chloroformi (5%), emulsio chloroformi (5%), chlorodyne, cremocarbonates—with no toxic results. Hepatotoxic effects are marked in habitual alcoholics, in whom chloroform must be avoided. As no other cheap anaesthetic agent may be readily available in outlying dispensaries and small hospitals or to general practitioners, the teaching to students of the correct methods of chloroform administration cannot yet be dispensed with. It would be a blessing if some method or drug were found which completely counteracted or prevented the toxic effects of chloroform. Sodium xanthine is said to protect against liver damage. In places where gas and intravenous barbiturates, or even ethyl chloride, are not yet easily available for all cases, the trouble and unpleâsantness of induction with pure ether and the large quantity of this agent needed with the open method in the great heat of summer, with consequent danger of convulsions, are all obviated by careful induction with chloroform, and its judicious use.—I am, etc.,

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## The So-called Meigs's Syndrome

SIR,—I read with interest the report by A. C. Clay *et al.* on two cases of fibroma of the ovary associated with hydrothorax and ascites (July 22, p. 113), but would like to protest against the name of Meigs, who only wrote of the condition in 1934, being associated with the syndrome. The description of this syndrome is by no means of recent origin, as I was told about it when I was a student 30 years ago, and have personally taught it to my students, as a rare possibility, for over 20 years. It is definitely recorded in Eden and Lockyer's *New System of Gynaecology*, published in 1917. If any name is to be associated with this syndrome, surely it should be that of the man who first described it, and, therefore, the name of either Cullingworth or Lawson Tait should be substituted.

The syndrome is certainly an uncommon occurrence, but I do not think nearly so rare as the recent literature on the subject would suggest. This is probably because, in this country at any rate, such cases are not commonly recorded in the medical journals, though most gynaecologists have encountered at least one case.—I am, etc.,

W. F. THEODORE HAULTAIN, F.R.C.S.Ed., F.R.C.O.G.
Edinburgh.

## Problem of the Small Bladder

SIR,—I have given particular attention to the type of case with chronic frequency that Mr. Sheppard mentions in your issue of July 22 (p. 124), and I have been able to benefit many of them after investigating the posterior urethra; for urethroscopy often shows that there is a chronic inflammatory process in the locality mentioned. This is so in spite of a sterile urine and absence of any indication on rectal examination that there is any pathological process present in this region.

In the male the common findings are small granulomata or polypi on the verumontanum or in one or other prostatic sinus, or small nodular projections (hillocks) on the lateral walls or roof of the posterior urethra. In many females with chronic frequency and in many children with enuresis—many of whom also have frequency—hillocks and polypi are also found in the posterior urethra. There seems good reason to believe that many of these lesions are the result of simple infections which occur insidiously in childhood.

The best urethroscope that I have found for these investigations in adults is the Joly examining (Charrière 24). It is important to avoid a large instrument. A good local anaesthetic should be used. In children I use a Gheringer type urethroscope (Charrière 16); a general anaesthetic is necessary for these.

In those cases in which the polypi, etc., are firm and fleshy destruction by fulguration with a weak current (1 unit on G-U machine) is necessary. In other cases gentle and intermittent dilatation of the posterior urethra regularly has a beneficial effect on the symptoms. For adult males well-softened gum-elastic bougies should be used at first after a good local anaesthetic; for adult females straight metal bougies; for children special curved metal bougies, under a general anaesthetic of course. Great care must be taken to see that the increase in size of the successive instruments used is finely graded. It is my custom with male adults not to take the dilatation above 26 Charrière (15 Eng.), except in special cases. Meatotomy is sometimes necessary before the patient can get the benefit of the larger sizes. In female adults I aim at 32 Charrière as the top size. The treatment of children is too complex to be dealt with here (see *Proc. roy. Soc. Med.*, 1944, **37**, 345). The benefit from dilatation is apparently in the promotion of drainage from the chronic inflammatory foci.

It is a most interesting study to examine some of these cases with the urethroscope after several dilatations and to note the improvement which has occurred. This often applies to gland orifices in the anterior urethra. Routine urethroscopy is most simply done in women. In adults the intervals between the dilatations should be gradually increased; my routine in an individual case is to give the dilatations at the following intervals: 3, 4, 6, 8, 12, 16, and 32 weeks. Over-frequent dilatation is certainly harmful.

I have come in contact with a number of patients who were discharged from the Services because of frequency or enuresis, whom I was able to help because of the urethroscopic findings.—I am, etc.,

H. P. WINSBURY-WHITE.
London, W.1.

## Site for Intramuscular Injection

SIR,—I have read with interest the letters of Prof. Grey Turner, Mr. Sydney Boyd, and Dr. Laughton Scott. Without entering into the controversy as to whether the buttock or the lateral aspect of the thigh is the better site, I think that three important points arise from their letters.

First, if the correct part of the buttock is used there should be no danger of injuring the sciatic nerve. The right site for an injection into the buttock is in the upper anterior quadrant an inch or two below the iliac crest. If this area is used the point of the needle will be at least as far from the sciatic nerve as it would be in the vastus externus. Secondly, wherever an intramuscular injection is given the needle must be long enough to pierce the overlying fat and reach the muscle. Thirdly, when it is intended that an injection should be intramuscular, before the plunger is pressed home it should be withdrawn to make sure that the injection is not going to be intravenous, no matter what the site of choice.

If these three points are granted then it would appear that these three writers are really criticizing technique rather than the site of injection, and therefore are pointing to the bad teaching of technique in this matter to students and nurses.—I am, etc.,

EVAN C. WYNNE-EDWARDS.
Hartford, Cheshire.

## Symptoms of Hiatus Hernia

SIR,—With reference to the excellent leading article on hiatus hernia (July 15, p. 83) may I mention an additional symptom which is quite amusing if somewhat unusual.

A very wealthy lady complained for years of substernal pain and heartburn. This was accentuated by the emotional stress of having to attend official dinners, to which function she was compelled by the social position of her husband. She also knew that she would experience a most distressing fullness and epigastric pain immediately at the beginning of the meal. Her medical advisers came to the conclusion that her complaint was a form of hysterical escapism from a loathsome duty. This view seemed confirmed by the story of the husband that the condition could be prevented and relief obtained if the patient had several glasses of champagne while dressing for the dinner.

Eventually, however, the diagnosis of a hiatus hernia was made by careful *x*-ray examination. The explanation of the effect of

champagne was that the carbon dioxide formed a gas bubble and the small herniated portion of the stomach was drawn back into the abdomen. I have seen the same effect achieved by giving soda-water.

The above story was told to me by my teacher and former chief, Dr. Julius Bauer, now professor of clinical medicine, Los Angeles, California.—I am, etc.,

London, S.W.3. V. C. MEDVEI.

## Chemotherapy in Otitis Media

SIR,—I am inclined to agree with Mr. G. H. Steele that general practitioners have had quite a lot of experience with sulphonamides in "these cases"—by which I mean acute otitis media—and when I say acute otitis media I do not mean "acute ears," "acute otitis externa," "acute catarrhal otitis media," "external haemorrhagic bullous otitis," "herpes oticus," or even "furunculosis meati." I mean acute otitis media. Moreover, the experience of some general practitioners in the use of sulphonamides has been sufficiently extensive under all conditions to enable them to speak with what Mr. Steele calls—not unreasonably—real authority. In my experience an otologist who has had no more than, as Mr. Dingley puts it, "at least a year of otoscopic experience" has still a long way to travel before he could be considered "competent to diagnose all the different varieties of acute otitis via the speculum," even with the added advantage of personal tuition and a selected series of cases. I would certainly not accept the opinion of such a gentleman without verification. It should be realized that since the introduction of the electric auriscope the general practitioner has become much more familiar with abnormalities of the drum, especially if he has the patience to carry out the toilet of the meatus. Failure to do this may lead him into errors of which he may later feel, as I have felt, heartily ashamed. The important thing is for him to be able to recognize a *normal* drum.

If sulphonamides *properly administered* bring about a subsidence of symptoms and resolution, surely it is an indication that they have been properly used and have effected their purpose. I absolutely deny that they can "mask symptoms" if they are given adequately in cases in which experience has proved them to be effective. The inept and pointless complimentary gesture which Mr. Dingley makes to the general practitioner by stating that his "valuable contribution" is in his "knowledge of his patient and the constitutional aspect of his illness" is of no more value than the knowledge of his patient and the constitutional nature of his illness are likely to be in the type of cases under notice—which is precisely *nil*.—I am, etc.,

Brookwood, Surrey. H. M. STANLEY TURNER.

SIR,—I have been extremely interested in the correspondence on this subject, and especially in the excellent article by Mr. A. R. Dingley (June 3, p. 747). The following case may be of interest in this connexion.

A few weeks ago I was asked to see a doctor's child aged 5, who had the following history. Five weeks previously the child had had an attack of tonsillitis followed seven days later by earache in the right and left ears. Sulphathiazole 0.25 g. four-hourly was given for two and a half days, but was discontinued owing to difficulty in getting the child to take the drug. There was slight otorrhoea from the left ear for three or four days and this cleared up. The right ear also discharged at this time—i.e., seven days after the onset of tonsillitis—and this appeared to clear up, but recurred several times and then appeared to clear up. One morning five weeks after the onset of tonsillitis the child complained of pain on lying on the right side, and it was noticed that the right ear was protruding outwards. I was then asked to see the child, and found a protruding right ear, and swelling and tenderness over the right mastoid. The right external meatus was full of thick creamy pus—a typical acute suppurative mastoiditis. The left ear was normal. Cortical mastoidectomy was performed. Very extensive suppuration was found; the whole of the mastoid cells were full of thick creamy pus. The tympanic membrane was thickened and oedematous and was incised at the same time. Recovery has been complete.

While this case did not have the requisite amount of sulphonamide therapy, what it had was given very early. I feel, however, that an early myringotomy may well have prevented the unfortunate sequel—viz., suppurative mastoiditis. It is my experience that early myringotomy followed by sulphonamide therapy gives the best results in otitis media, and I am in complete agreement with all that Mr. Dingley has so admirably explained.—I am etc.,

Poole, Dorset. A. MACKENZIE ROSS.

## Septic Tonsils in the Soldier

SIR,—Major-Gen. Philip Mitchiner (July 8, p. 37) writes: "Tonsillectomies and operations on the nasal septum undoubtedly constitute scalps for the operating surgeons, but how often do they make the patient any more fit for full duty in the rough and tumble of Service life?" The statement made here is a gratuitous insult to E.N.T. surgeons. Most of us will not think very highly of a surgeon, however distinguished, who looks on his operations as "scalps." But the question raised is more important, and one aspect of it is of immediate interest. As an E.M.S. surgeon I have been disagreeably surprised to find soldiers evacuated from France for tonsillitis, a preventable disease, and others with various "rheumatic" conditions associated with septic tonsils. Are we to do nothing for them?—I am, etc.,

E. S. BURT HAMILTON.

## Episiotomy

SIR,—As a mere G.P. I hesitate to challenge Dr. Josephine Barnes's criticism (July 1, p. 23) of my memorandum of June 17 (p. 813). This article was written from the standpoint of domiciliary midwifery, and I am sure Dr. Barnes will admit that conditions of work are often very different from those obtaining in hospital.

The method illustrated was developed primarily to secure accurate apposition of the wound edges, and not necessarily to avoid anaesthesia after the birth. Personally (and here I would welcome the views of other general practitioners) I have long given up using catgut in the perineum, owing to the risk of sepsis, but such stitches, if considered necessary, could, of course, be inserted after the birth.

I am aware of the dangers attending the use of chloroform in the third stage, and never employ a general anaesthetic other than nitrous oxide. Finally, I am glad to have it confirmed on such good authority that there is a wider scope for episiotomy.—I am, etc.,

Borrowash, Derbyshire. G. S. NEILSON DOW.

## Riboflavin and Allied Deficiencies

SIR,—The very mass of writing on the vitamins, of which the lecture by Dr. Stannus (July 22, p. 103) is an impressive example, can be confusing to the practitioner. The difficulty is to apportion the appropriate role to each of the vitamins essential for the release of energy from carbohydrate. There are observations which suggest that riboflavin is its own cytochrome and acts as such when the usual cytochrome (haemin) is not available, as in avascular structures. A very early sign of ariboflavinosis is vascularization of the cornea; the oxygen-carrying haemin has to be brought in to maintain the life of the cornea, and it is withdrawn as soon as riboflavin is supplied in sufficient quantity.

The main purpose of carbohydrate metabolism, however, is the production of the form of energy known as muscular work; for this haemin is the cytochrome and ascorbic acid the main vitamin essential for each of the six steps of hexose breakdown. $B_1$ is a specific catalyst in degradation of pyruvic acid, a by-product of this reaction, and nicotinic acid is necessary for the utilization and elimination of lactic acid. Riboflavin also aids oxidation of carbohydrate, lactic acid, amino-acids, and aldehyde, but there is little evidence that it is concerned with the production of muscular work. This possibly is reflected in the relative daily requirements of riboflavin (1.5 mg.) and ascorbic acid (50 mg.+).

The particular role of riboflavin in carbohydrate metabolism is probably concerned with maintaining structure as contrasted with function, for all the manifestations of ariboflavinosis quoted by Stannus are dissolutions *of structure*. If we compare this with the Crandon experiment we note that muscular weakness was apparent long before there was any structural damage, and that muscular strength returned immediately ascorbic acid was added to the diet.

The conclusion therefore is that riboflavin is necessary for that part of carbohydrate metabolism concerned with structure, but that it is only indirectly concerned with the conversion of glucose into muscular work.—I am, etc.,

Caernarvon. GRIFFITH EVANS.

### Epidemiology of Infective Hepatitis

SIR,—In Prof. L. J. Witts's interesting discussion of some problems of infective hepatitis in your issue of June 3 it was stressed that no animal is known which can be experimentally infected with the disease and that the discovery of such an animal would very greatly facilitate the epidemiological study of the condition. The following observation, which was made during the last war, may therefore be of interest. At Abbeville I saw a nursing sister who was convalescent from "catarrhal jaundice," and also, seated upon her shoulder, a small pet monkey. The animal at that time was undoubtedly jaundiced, and it had been in contact with the nurse during the acute phase of her illness. Unfortunately I am unable to name the species of monkey concerned, and the conjunction of the two cases may, of course, have been a mere coincidence; on the other hand the incident may possibly afford a clue to the discovery of the animal which would be so helpful in elucidating the aetiology of a disease which is causing much temporary disablement at the present time.—I am, etc.,

Southwell, Nottinghamshire. C. H. WARNER.

### Self-medication and Patent Medicines

SIR,—The article on self-medication and patent medicines (July 15, p. 87) is certainly timely, but it would have carried more weight had the number of persons questioned been greater, and if it could have been demonstrated conclusively that the medicine addicts were more unhealthy than the abstainers, or that the educated were more abstemious in the matter of drugs than the ignorant. I was thankful to find that the inquirer was tactful enough to limit his questioning to the consumers of medicine *not* taken under medical direction, otherwise the results would have been rather embarrassing.

I wonder, out of all the millions who imbibe purgatives, lubricants, anodynes, stomach medicines, etc., how many are really harmed, except financially. Compared with the pleasure derived the harm done must be negligible. Has it ever been proved, for instance, that the achlorhydria encouraged by prolonged ingestion of paraffin and alkalis has anything to do with the incidence of gastric cancer?

I can't see how, in a democracy, one can do much by legislation to curb the advertiser's flights of fancy, and why should one want to? Life is drab enough anyway. Why should the advertisers be limited to the truth any more than politicians or doctors?

In spite of the findings of Edwards and Kinsie, and the fact that believers on the whole are happier, fatter, and psychologically sounder than sceptics, education surely should be some little help in assisting us to discriminate between the fantastic and the possible. But how to set about this education? It is no good trying to enlist the aid of the Press, for they are hardly likely to bite the hand that feeds them. Fiction had a good shot at it in Wells's *Tono Bungay*, which, by the way, should make an admirable film. What about the B.B.C.? Unlike other radio systems, it at least has the advantage (we hope) that it doesn't suffer from vested interests. I should say this is broadcasting's big chance.—I am, etc.,

Thame, Oxford. E. GRANGER.

### Varicella and Herpes Zoster

SIR,—The cases of Drs. F. M. B. Allen and J. J. Manning (July 22, p. 115) have reminded me of a case of my own which had one or two additional points of interest.

The patient was a man aged 81. In 1934, when he was 73 years of age, he developed exfoliative dermatitis, which appeared to be intractable to any form of treatment and involved the whole of his skin surface. In 1935, without any preliminary symptoms, he had an acute retention of urine; his prostate proved to be grossly enlarged. He was considered to be a particularly bad operative risk on account of his skin condition, but, apart from it, he was extremely vigorous, both mentally and physically. His temperament was such that a catheter life would have been an intolerable burden, and accordingly the risks of operative treatment were faced. After a preliminary suprapubic drainage the prostate was removed, and, following a stormy passage of a week or so, he made a complete recovery with excellent control and a clean bladder. A few weeks after his operation the exfoliative dermatitis cleared up.

On April 9, 1942, the patient's 81st birthday, I was called in to see him and found that he had a typical band of herpes zoster of about the sixth or seventh right dorsal distribution with the usual burning sensation and pain. He was kept in bed and exactly a week later a chickenpox eruption of moderate severity appeared. The distribution of the vesicles was in no way unusual and the scalp had quite a number. On April 25 his grandson aged 8, who lives in the same house, developed chickenpox, and about ten days later his granddaughter, aged 4, followed suit. The boy had a mild attack which ran a normal course. The little girl's attack was rather more severe with a comparatively large number of vesicles on the face. My original patient recovered from his herpes zoster, and, though he suffered from recurring pain in the area for several months, he was able to resume his bowls, his club, and other activities.—I am, etc.,

Preston. F. M. ROSE.

SIR,—With reference to the two cases reported by Dr. Allen and Dr. Manning may I add yet another within my own experience.

On Dec. 11, 1942, I saw a normally very healthy man aged 40 with a profuse herpetiform eruption involving the right side of the neck and shoulder. By Dec. 22 a typical varicella was established. The noticeable point of difference in these three cases is the sequence. According to Dr. Allen's record the herpes followed the varicella after an interval of about three weeks. In Dr. Manning's case the two conditions were strictly concurrent, while in my own the varicella followed hard upon the heels of the herpes.—I am, etc.,

Yeovil. NORMAN FLOWER.

### Adoption of Children (Regulation) Act, 1939

SIR,—This Act provides that, if arrangements are being made for a child under 9 years of age to be placed in the care and possession of a person who is not the child's parent or guardian or near relation, any third party participating in such arrangement must give seven days' notice to the Welfare Authority before the child is transferred to the adopter.

Recently a doctor attended a patient on the birth of her illegitimate child, and also attended a married woman who had been disappointed by the birth of a stillborn child. He introduced the two women with a view to the adoption of the illegitimate child by the married woman. Subsequently the practitioner's attention was drawn by the Welfare Authority to his failure to give the notice required by the regulations; happily, through the intervention of the Medical Defence Union, the matter was brought to a satisfactory conclusion.

The purpose of this letter is to bring to the notice of doctors, nurses, and midwives an obligation of which many may be unaware.—I am, etc.,

JAMES FENTON,
London, W.C.1. President, Medical Defence Union, Ltd.

### Character and Personality in the Medical Student

SIR,—Dr. R. John Gourlay (July 15, p. 96), for some obscure reason, appears to think I advocate a classless society. Let me assure him that this is far from being so and that I heartily agree with the greater part of his letter. Also I would like to join with him in praising ability, but not only as manifest in "our men of ability" but also in all its many other forms.

All that I ask is that ability is given a fair chance. If the dustman's son wishes to become a doctor, and is able, let him be given every facility to succeed. At the same time if the doctor's son wishes to become a doctor, and is unable, let him find an occupation more suited to his ability. The laws of heredity and the theory of evolution remain unchallenged and irrelevant. Let ability, not wealth, be the key to success and social distinction. Hitherto wealth has been the key and ability has merely turned it in the lock. Ability by itself has been all but impotent. It would be impertinent to ask how many doctors would be in their present eminent positions if they had not had the money to provide for their education; their ability, inherited or not, by itself would have availed them as little as does that of millions of the other members of the community. If ability is given every chance in its own right

it is immaterial whether or not it results from inheritance or environment.

So long as ability is subordinate to wealth on the road to success and eminence, just so long will our standards of eminence remain mere shadows of what they might be. And wealth will remain the source of wealth, making real progress impossible.

Finally, let me assure Dr. Gourlay that far from putting the clock back 2,000 years I am attempting to push it round a little faster than, regrettably, many would have it go.—I am, etc.,

Park Prewett Hospital. H. E. VICKERS.

### Ophthalmologist and Optician

SIR,—As a general practitioner who also derived an income, before medical qualification, as a refractionist I should like to add a suggestion to the contribution of your correspondent Dr. Geoffrey Ebbage. I have always found that opticians have great difficulty in *not* prescribing lenses, and only the few conscientious refractionists refer their patients to the medical practitioner. I suggest that: (*a*) the training and examinations in refraction and orthoptics should be intensified, and the recognition of organic disease minimized, and (*b*) that opticians should treat only those patients who have been seen and examined by their medical adviser and referred to the optician.—I am, etc.,

Silford. BERNARD WILKINS, M.B.

# Obituary

## B. J. BRANDSON, M.D., F.C.P.S.CAN.

Dr. Brandur Jonsson Brandson, professor emeritus of surgery, died at his home in Winnipeg on June 20. Few doctors in Western Canada have been more widely known and deeply loved or have exercised a greater influence among their own people in the field of medicine.

Born in Iceland on June 1, 1874, he came with his parents to Minnesota at the age of 4. He graduated in arts from Gustavus Adolphus College at St. Peters, Minn., and in medicine from Manitoba Medical College in 1900. For five years, interrupted by a year in Great Britain, he practised at Edinburg, N.D. With his life-long friend, Dr. O. Bjornson, he returned to Winnipeg in 1905. For a time they practised in partnership, but later each took the line of work for which he was specially fitted. Dr. Bjornson became professor, then emeritus professor, of obstetrics, while Dr. Brandson rose by successive steps to be lecturer in surgery, associate professor, professor, head of the department of surgery 1927-34, and, on his retirement, emeritus professor. At the convocation last May the University of Manitoba conferred on him the degree of Doctor of Laws *honoris causa*. This is not the first honorary degree granted him. In 1930 he was appointed a representative from Canada to attend the millennium of the Althing, the Icelandic parliament. At Reykjavik the University of Iceland conferred the honorary degree of Doctor of Medicine. Five years later the Icelandic Government made him a Grand Knight Commander of the Royal Icelandic Order of the Falcon. At the 98th Annual Meeting of the British Medical Association, held in Winnipeg in 1930, Dr. Brandson was one of the vice-presidents in the Section of Surgery. The Winnipeg Medical Society granted him life membership in 1943. He was a Fellow of the American College of Surgeons, and a Charter Fellow of the College of Physicians and Surgeons of Canada. In his arts college Dr. Brandson had as his friend and classmate the late Thomas H. Johnson, who also went to live in Winnipeg and became Attorney-General of Manitoba. Though Brandson took a keen interest in politics and was repeatedly urged to contest an electoral district, he never allowed his name to go for nomination. At the time of his death he was honorary president of the First Lutheran Church, Winnipeg. An institution very dear to his heart was the Icelandic Old Folks' Home at Gimli, the "Home of the Happy Sunset." He is survived by his widow, two daughters, and a son. One daughter is the wife of Major John A. Hillsman, R.C.A.M.C. overseas. The son, Lieut. Thomas L. Brandson, is believed to have been serving as paymaster on H.M.C.S. *Athabaskan*, sunk recently in conflict with German destroyers in the English Channel.

In addition to his early postgraduate year in Great Britain and the Rotunda, Dublin, he also studied in London and Vienna. He was a foremost surgeon, possessing that greatest of surgical qualities—sound judgment. His enduring fame, however, will be his gifts as a teacher. Wise, prudent, humane, and above all kindly, he will be long remembered. R. M.

Dr. JOHN MURDOCH died on July 7 at his home in Chesham Place, Brighton, aged 62, after a long illness. He graduated M.B., Ch.B.Glas. in 1904 and took the F.R.C.S.Ed. in 1909. Leaving his practice in Kinross in 1914 he went to France, where he served with great gallantry, gaining the Military Cross as a combatant officer in the Argyll and Sutherland Highlanders. He was wounded and invalided out of the Army in 1916. He resumed the practice of medicine by joining the Red Cross in 1917, which he served until 1939, most of which time in the office of Commandant of the Red Cross Hospital for Officers, Brighton. In this capacity he devoted the whole of his energies to the well-being of the ex-officers under his care, and will long be remembered for his integrity and devotion to duty. He leaves a widow and two sons, both of whom are serving in the Army over-seas.—G. W. B.

We regret to announce the death on July 22 of Mr. ERNEST WARE, emeritus surgeon to the Hospital of St. John and St. Elizabeth in St. John's Wood, and to the Hampstead Hospital for Children. Ernest Edwin Ware had his medical training at St. Thomas's Hospital, and after qualifying in 1889 was house-surgeon there. He graduated M.B., B.S.Lond. in 1891, and took the M.D. in 1893. Before settling down in surgical practice in North-West London Ernest Ware was for a time medical officer at St. Mary's Hospital for Children at Plaistow, and resident medical officer at the East London Hospital for Children, Shadwell. He was a past chairman of the Hampstead Division of the British Medical Association, and the Hampstead Medical Society, in whose work he had taken an active part for many years, made him an honorary member. He was elected F.R.C.S.Eng. in 1930 and the National University of Ireland gave him the honorary degree of M.Ch. in 1938. Another distinction, but not a medical one, which he prized was admission to the Order of Knights of St. Gregory. The Hospital of St. John and St. Elizabeth, where he had given such long and faithful service as visiting surgeon, held a requiem for him in the chapel on July 26.

Dr. J. W. HYSLOP, who died on July 13 in his 75th year, was the son of the Rev. J. S. Hyslop and was born in Leven, Fifeshire. He studied medicine at Edinburgh University, where he graduated M.B., C.M. in 1893. He was in general practice in Menston, near Leeds, for some 50 years. His interest in village life was always great and varied. He was the founder and for many years president of the Menston Amateur Operatic Society, and his keenness and organizing ability did much to make this a most successful venture with far more than a local reputation. He was also a founder of the Menston Sick Nursing Society and its secretary for many years. He held the post of superintendent of the Menston Isolation Hospital for 37 years, and only retired in June of this year. His work there was perhaps his crowning achievement, for I have never known a happier hospital. Many of the children under his care were loath to leave when their time was up, and I have heard several children ask to be taken back on the slightest pretext. The results of treatment at the hospital were excellent, bearing comparison with any in the country. In 1921 Dr. Hyslop was appointed a Justice of the Peace, and in recognition of his scrupulously fair dealings as a magistrate at Otley court he was recently appointed chairman of the Juvenile Panel. As a general practitioner he gained the confidence of his patients by his untiring devotion and care. Menston was indeed fortunate to have Dr. Hyslop as its family doctor.—R. J. G.

We regret to announce the death on July 19 at St. Asaph of Dr. HENRY LLOYD, who had been a member of the B.M.A. since 1892, served on the Welsh Committee for one term, and twice represented his Division at Annual Meetings. He studied medicine at Liverpool and University College Hospital, qualifying in 1884 and taking the M.D. degree of Durham University in 1900. When at the end of 1937 he resigned his position as district medical officer, public vaccinator, and medical officer of the St. Asaph Public Assistance Institution, he was the doyen of the medical profession in the Vale of Clwyd, and his resignation was received with much regret by the Flintshire County Council.

Dr. Arthur F. Perigal writes from Hatfield: May I be permitted to add my humble appreciation of Sir WILLIAM LISTER, whom I knew well in 1898, when he was with Marcus Gunn and I a clinical assistant at Moorfields with him. Handsome, debonair, and kind, he was ever ready to explain and help, and was indeed a conscientious and accurate worker in spite of fatigue after some 4 or 5 hours in the vitiated atmosphere of that out-patient department. Later he was most charming and considerate to private patients sent to him, whatever their status; the memory of his friendship is most happy.

# The Services

## CASUALTIES IN THE MEDICAL SERVICES

Squad. Ldr. ROBERT GORDON SHARP GRANT, who was killed on June 6 on the Normandy beaches, aged 32, studied medicine at Edinburgh University and graduated M.B., Ch.B. in 1938. After holding house appointments at the Royal Infirmary, Edinburgh, and Seafield Maternity Hospital, he was appointed to a commission in the medical branch of the Royal Air Force Volunteer Reserve on June 25, 1940.

*Died of wounds.*—Major R. R. Maitland, R.A.M.C., Lieut. W. H. Black, R.A.M.C.

*Wounded.*—Temp. Lieut.-Col. W. J. Young, I.M.S.; War Subs. Capts. M. S. Howe, W. R. C. Lang, and R. J. Waugh, and Temp. Major E. R. Smith, R.A.M.C.

*Missing.*—Capt. R. A. B. Kinloch, R.A.M.C.

## DEATHS IN THE SERVICES

Surg. Rear-Adml. GUY LESLIE BUCKERIDGE, C.B., O.B.E., who died in London on July 14, was born in 1877 and qualified M.R.C.S., L.R.C.P. from Guy's Hospital in 1903, and then joined the Navy as a surgeon. He served at Osborne and at sea in the last war, afterwards became Deputy Director-General of the Medical Department at the Admiralty, and was later in charge of the Royal Naval Hospital, Haslar, retiring in 1937. During the later years of his service he was Honorary Surgeon to the King. Admiral Buckeridge had joined the B.M.A. in 1920, and while at Haslar was elected an associate member of the Portsmouth Division. Dr. G. de Swiet sends the following tribute: The passing of Surgeon Rear-Adml. G. L. Buckeridge has robbed the Willesden No. 1 National Service Medical Board of its beloved chairman. It was a privilege to be ruled by such genuine kindness and amiability during these five weary years of stress and sorrow. The great responsibility of one's task was often lightened by "the Admiral's" perfect tact, unfailing good humour (in spite of indifferent health), and his broad-mindedness. He was an exceptionally well-read man, and for a medical man he possessed an unparalleled knowledge of European literature of the classical type, especially Russian and French. He was equally well versed in philosophy and history, and a brief chat with him on any of these and any other subject—between the "cases"—went a long way towards relieving the inevitable pressure and monotony of work. When occasion occurred he was ready to wield a subtle and satirical pen, raised against harshness or incompetence. He was incapable of arousing enmity, for he was disarmingly quick in admitting an error and making amends. His frail physique and gentle yet worldly manner gave one infinitely more the impression of a courtier than of a sailor. Both doctors and clerks have the sense of a deep and irreplaceable loss.

# Medical Notes in Parliament

### Cancer: Service Pensions

In the House of Commons on July 25 Mr. LIPSON drew attention to the refusal of the Minister of Pensions to grant pensions to two men who had been discharged from the Services suffering from cancer. Sir WALTER WOMERSLEY, replying, said he must take the consensus of medical opinion in arriving at a decision whether a certain disease was due to or had been aggravated by service. It was inevitable that cancer might, from time to time, show itself during service, and his Department had to consider whether or not service had played any part in its onset or development. Although the actual cause of cancer was not known, there had for a long time been a general medical agreement on certain conditions which might possibly be related to its onset and also on other conditions which were certainly not so related. The Medical Research Council, at the request of his Department, convened a conference of experts, which gave comprehensive advice on the conditions affecting different forms of cancer and the sites in which they occurred, and this advice could be taken as constituting a consensus of medical opinion. It was, in general, to the effect that it was only in exceptional cases that the development of cancer might possibly be attributed to, or influenced by, a previous injury or disease arising out of war service, and certain criteria were laid down as affording a basis for decision. Each case of cancer was considered by his Department in the light of this advice, and, although it had not been possible to accept the vast majority of cases, yet, in an appreciable number, where a reasonable doubt could be said to exist, entitlement had been conceded. So it was not true to say that the Ministry had not granted pensions even for cancer if circumstances warranted it.

Colonel CLARKE asked if failure on the part of a medical officer to diagnose cancer, with the result that the man was treated wrongly and lost his life, was not considered an aggravating cause. He said he had heard of cases where men had been wrongly diagnosed, had been treated for something else and had died. Sir WALTER WOMERSLEY: If it were a case of wrong diagnosis and that was shown to me clearly as the reason for a man's life being shortened, it would be a case for pension.

### Finance of the White Paper

Replying in the House of Lords on July 20 to a debate on the cost of social reform, Lord WOOLTON said that to maintain a higher standard of health the country would have to find for the early years of the National Health Service, £148,000,000 a year from rates, taxes, and contributions from the Insurance Fund. Before the war the cost to public funds was £61,000,000. Of the increase, some £40,000,000 must be reckoned as transferred from one type of payment to another. Some of the remaining difference must be attributed to the rise in prices. At current rates of absence from work through sickness the loss might amount to £280,000,000 per annum. Present rates of absenteeism were high as a result of long hours, the number of married women in industry, and the withdrawal of the younger men to the Forces. The loss which might be expected in a year after the war was £180,000,000 unless the standard of health could be improved. The expenditure proposed in the White Paper on the Health Services would, he believed, prove a profitable expense.

*Inquiry into Veterinary Practice.*—Mr. Robert Hudson and Mr. Tom Johnston have appointed a committee to inquire into the extent and effect of veterinary practice in Great Britain by persons who are not registered veterinary surgeons and to make recommendations as to any measures which may be desirable to limit or regulate such practice. Its members are: Sir John Chancellor (chairman), Mr. A. C. Brown, Sir Daniel Cabot, Mr. J. W. Salter-Chalker, Mr. Charles Dukes, Prof. James Gray, Mr. C. M. Holmes, Mr. W. F. Holmes, Mr. Robert Hobbs, Mr. W. D. Jackson, Sir Louis Kershaw, and Lieut.-Col. P. J. Simpson.

*Penicillin: Large-scale Manufacture.*—On July 25 Mr. SALT asked the Minister of Supply whether, in view of the desirability of removing all obstacles to the rapid development of the large-scale manufacture of penicillin, he would now agree to permit full publicity with regard to the methods of manufacture and withdraw those objections hitherto raised on security grounds. Mr. CHARLES PEAT, who replied, said he was not aware that large-scale production of penicillin was being impeded through lack of information. The general method of manufacture had been published in the technical press.

*Blind Persons in Industry.*—On July 25 Mr. THORNE asked the Minister of Health the number of blind persons in the United Kingdom, how many were fully employed, and what reports he received on the degree of satisfaction given by them at the place of employment. Miss HORSBRUGH said that on March 31, 1943, the latest date for which figures were available, the number of registered blind persons in the United Kingdom was about 90,000. About 10,000 were employed or working on their own account, but some of these (perhaps 1,000) were part-time workers only. She was informed by the Minister of Labour that the reports on blind persons engaged in ordinary industry were very satisfactory.

*Intelligence Tests for Army.*—On July 25 Sir JOHN GRAHAM KERR asked the Secretary of State for War whether, in view of the increased recognition of the importance of a high standard of powers of observation and of general mental alertness, he would institute adequate examination tests in these for all candidates for commissions in the Army. Sir JAMES GRIGG said that all recruits on entering the Army and all candidates for commissions were given intelligence tests which measured their mental alertness. Candidates for commissions who passed through War Office Selection Boards and this covered all but a small number who were commissioned directly into technical arms—were given practical tests which measured their powers of observation and their mental alertness. The importance of these qualities was fully appreciated.

*Output and Working Hours.*—Mr. ROSTRON DUCKWORTH on July 27 asked Mr. Attlee whether, as the report of the Industrial Health Research Board could not state whether reduced working hours increased or decreased output, he would arrange for the Medical Research Council to continue its investigations along the same lines. Mr. ATTLEE said the Industrial Health Research Board of the Medical Research Council proposed to investigate this subject further as opportunity permitted. It had been firmly established that, except for brief periods of special emergency, working hours in many operations should not exceed 60 to 65 for men and 55 to 60 for women. The point not yet decided conclusively was whether reduction of working hours below those limits had a further beneficial effect measurable in terms of output. The report indicated the practical difficulties in reaching a clear decision on this question by investigations carried out under the unstable conditions of wartime.

### *Notes in Brief*

The committee appointed by the Medical Research Council to investigate jaundice has collected much information, but the causes of the disease are still not fully known. Research in being continues.

# Medical News

The Conjoint Committee of Epsom College will in November award an annuity of £35 per annum to a spinster daughter of a medical man. Candidates must be Protestants and fully 65 years of age. Forms of application may be had from the Secretary's Office, Epsom College, Epsom, Surrey, and must be returned by the morning of Oct. 25.

The Mental After-Care Association (Eagle House, 110, Jermyn Street, S.W.1) will broadcast in the "Week's Good Cause" on Sunday next, Aug. 6, at 8.25 p.m.

The address of the Drugs Branch, Home Office, is now 52, Prince's Gate, South Kensington, S.W.7.

Dr. Sidney Osborn, medical officer in charge of First Aid Post, Civil Defence Casualty Service, Ipswich, has been commended for brave conduct in Civil Defence.

A notice issued by the Pharmacopoeia Commission states that potassium sulphate *British Pharmacopoeia*, 1914, may be used in place of lactose in making pulvis ipecacuanhae et opii, and that sucrose may be used, also in place of lactose, as diluent in making pepsinum and pancreatinum.

British Medical Association House, including the Library, will be closed on Saturdays during the month of August.

## EPIDEMIOLOGICAL NOTES

### Discussion of Table

In *England and Wales* during the week there was very little change in the trend of infectious diseases. Notifications of diphtheria and dysentery were respectively 66 and 22 higher than last week. Pneumonia notifications fell by 102, and measles by 35. In Durham diphtheria notifications went up from 43 to 70, the cases being widely distributed throughout the county.

The chief local returns of dysentery were: Glamorganshire 49 (Cardiff C.B. 15); Sussex, Hailsham R.D. 17; Southampton 24 (Hartley Witney R.D., 12); Lancashire 12; Essex 10.

In *Scotland* 20 more cases of dysentery were reported than last week, but there were 61 fewer cases of acute primary pneumonia. The incidence of diphtheria remained at the same low level as last week. The rise in dysentery was due to Lanark County, where the cases rose from 5 to 18. Edinburgh reported 14 cases and Glasgow 10.

In *Eire* measles notifications dropped to almost half the high level of the previous fortnight. Over half the reported cases were in Co. Clare, Ennis U.D.

### Tuberculosis in London

On July 27 Mr. Willink announced the figures for tuberculosis mortality in the administrative county of London for the past nine years. The rates were:

*Death Rates from Tuberculosis (All Forms) per 1,000 Population, 1935–43 (excluding Non-civilians from Sept. 3, 1939)*

| | Rate per 1,000 | |
|---|---|---|
| 1935 | 0.746 | Based on total deaths and total population |
| 1936 | 0.755 | |
| 1937 | 0.771 | |
| 1938 | 0.704 | |
| 1939 | 0.760 | Excluding non-civilians from Sept. 3, 1939 |
| 1940 | 0.974 | Based on civilian deaths and civilian population |
| 1941 | 1.248 | |
| 1942 | 1.017 | |
| 1943 | 0.984 | |

Mr. Willink said that these figures represented the deaths of both sexes and at all ages from tuberculosis per 1,000 total population up to Sept., 1939, and per 1,000 of the civilian population after that date. They did not indicate the trend of tuberculosis mortality in London, because (1) great changes had occurred since 1939 in the sex and age proportions of London's population; and (2) medical selection for the Services left behind the bulk of tuberculous persons in the civilian population. Death rates for separate sex–age groups, which alone could indicate the real trend of mortality, could not be calculated for local areas for years since 1939, because the requisite populations were not known in detail of sex and age.

### Week Ending July 22

The returns of infectious diseases in England and Wales during the week included: scarlet fever 1,461, whooping-cough 1,157, diphtheria 471, measles 2,401, acute pneumonia 374, cerebrospinal fever 46, dysentery 151, paratyphoid 4, typhoid 21.

No. 28

## INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended July 15.

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland.

*Figures of Births and Deaths, and of Deaths recorded under each infectious disease, are for:* (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

| Disease | 1944 (a) | (b) | (c) | (d) | (e) | 1943 (Corresponding Week) (a) | (b) | (c) | (d) | (e) |
|---|---|---|---|---|---|---|---|---|---|---|
| Cerebrospinal fever | 59 | 4 | 20 | 5 | 1 | 51 | 5 | 20 | 2 | 3 |
| Deaths | | 1 | — | | | | — | 1 | | |
| Diphtheria | 491 | 24 | 89 | 74 | 8 | 571 | 37 | 131 | 76 | 26 |
| Deaths | 3 | 2 | — | — | 1 | 8 | — | — | 2 | — |
| Dysentery | 156 | 9 | 68 | 1 | — | 160 | 7 | 125 | — | — |
| Deaths | | | | — | — | | | | — | — |
| Encephalitis lethargica, acute | 4 | — | — | — | — | 1 | — | — | — | — |
| Deaths | | — | | | | | — | | | |
| Erysipelas | | | 25 | 5 | 1 | | | 29 | 11 | 1 |
| Deaths | | 1 | | | | | — | | | |
| Infective enteritis or diarrhoea under 2 years | | | | 14 | | | | | — | |
| Deaths | 41 | 3 | 13 | 6 | — | 45 | 10 | 9 | 8 | 4 |
| Measles* | 2,536 | 130 | 61 | 130 | 35 | 3,054 | 155 | 49 | 29 | 6 |
| Deaths | 2 | 1 | — | — | — | — | — | — | — | 1 |
| Ophthalmia neonatorum | 65 | 3 | 11 | — | — | 89 | 2 | 28 | — | — |
| Deaths | | | | | | | | | | |
| Paratyphoid fever | 7 | — | 3(B) | — | — | 11 | 1 | 2 | — | — |
| Deaths | — | — | — | — | — | — | — | — | — | — |
| Pneumonia, influenzal† | 437 | 25 | 4 | — | 2 | 457 | 30 | 10 | 1 | 3 |
| Deaths (from influenza) | 11 | 1 | — | — | 1 | 4 | — | — | — | — |
| Pneumonia, primary | | | 118 | 19 | | | | 145 | 10 | |
| Deaths | | 20 | | 6 | 5 | | 17 | | 6 | 4 |
| Polio-encephalitis, acute | 3 | — | | | | 2 | — | | | |
| Deaths | | — | | | | | — | | | |
| Poliomyelitis, acute | 16 | 1 | 4 | — | — | 7 | 1 | — | 1 | — |
| Deaths | | — | | | | | — | | | |
| Puerperal fever | | — | 11 | | — | | 1 | 17 | | — |
| Deaths | | | | | | | | | | |
| Puerperal pyrexia‡ | 141 | 6 | 6 | 1 | 1 | 154 | 9 | 10 | 1 | — |
| Deaths | | 1 | | | | | 1 | | | |
| Relapsing fever | — | — | | | — | — | — | | | — |
| Deaths | | | | | | | | | | |
| Scarlet fever | 1,394 | 56 | 167 | 22 | 58 | 2,082 | 196 | 191 | 57 | 31 |
| Deaths | 1 | 1 | — | — | — | 1 | — | — | — | — |
| Smallpox | — | — | — | — | — | — | — | — | — | — |
| Deaths | | | | — | — | | | | — | — |
| Typhoid fever | 8 | — | 2 | 10 | — | 11 | 1 | 1 | 3 | — |
| Deaths | — | — | — | — | — | — | — | — | — | — |
| Typhus fever | — | — | — | — | — | — | — | — | — | — |
| Deaths | | | | — | — | | | | — | — |
| Whooping-cough* | 2,323 | 181 | 56 | 25 | 11 | 2,110 | 117 | 74 | 32 | 34 |
| Deaths | 4 | 1 | 3 | — | 1 | 7 | 2 | 3 | 1 | — |
| Deaths (0–1 year) | 284 | 35 | 63 | 31 | 11 | 286 | 42 | 45 | 30 | 23 |
| Infant mortality rate (per 1,000 live births) | | | | | | | | | | |
| Deaths (excluding still-births) | 4,163 | 830 | 542 | 165 | 95 | 3,790 | 492 | 517 | 164 | 130 |
| Annual death rate (per 1,000 persons living) | | | 12·5 | 10·7 | § | | | 11·7 | 10·8 | § |
| Live births | 7,389 | 838 | 958 | 366 | 242 | 6,502 | 782 | 938 | 398 | 272 |
| Annual rate per 1,000 persons living | | | 19·5 | 23·7 | § | | | 19·1 | 26·2 | § |
| Stillbirths | 205 | 10 | 30 | | | 207 | 27 | 26 | | |
| Rate per 1,000 total births (including stillborn) | | | 30 | | | | | 27 | | |

* Measles and whooping-cough are not notifiable diseases in Scotland, and the returns are therefore an approximation only.

† Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

‡ Includes puerperal fever for England and Wales and Eire.

§ Owing to evacuation schemes and other movements of population, birth and death rates for Northern Ireland are no longer available.

# Universities and Colleges

## UNIVERSITY OF CAMBRIDGE

The following candidates have been approved at the examinations indicated:

FINAL M.B.—*Part I* (Surgery, Midwifery, and Gynaecology): P. Allebone, J. D. Andrew, T. C. Beard, M. F. Bethell, D. G. Bratherton, G. N. Cooke, G. S. Crockett, J. M. Davis, C. H. de Boer, H. J. Dismorr, E. J. Dowling, J. A. Dudgeon, M. A. Epstein, G. L. Evans, T. P. S. Frew, J. S. R. Golding, B. A. J. C. Gregory, P. F. Haggart, D. W. Hall, F. G. J. Hayhoe, P. R. Headley, E. W. Heining, A. Hill, S. M. Hilton, J. G. Holmes, W. R. Horsfall, E. G. Jenner, E. D. Jones, J. D. S. Knight, W. Kwantes, K. W. Leech, J. R. May, E. T. G. Meade-Waldo, D. J. Morton, J. P. D. Mounsey, E. W. Nation, G. A. Newsholme, M. Newton, M. B. Paul, G. F. Roberts, J. M. Roberts, P. K. Robinson, F. S. Sinker, C. A. Storr, J. M. Stowers, J. M. Thomas, K. Till, B. H. Vawdrey, M. H. D. Veale, P. R. Westall, D. Wilkes, R. J. Williams, L. Wolman, M. F. T. Yealland, G. Yerbury. *Women:* E. M. Davies, M. H. Jordan.

*Part II* (Principles and Practice of Physic, Pathology and Pharmacology): T. S. L. Beswick, R. H. Boardman, D. G. Bratherton, D. Brazier, A. Comfort, G. S. Crockett, P. D. B. Davies, P. J. De Vescovi, J. A. Dudgeon, D. A. W. Edwards, M. A. Floyer, P. H. Friedlander, J. W. Fullerton, C. R. H. Green, J. A. Harrington, C. E. Hartley, S. M. Hilton, R. F. Hollick, N. S. Hooton, W. R. Horsfall, G. I. C. Ingram, R. E. Irvine, J. Lorber, M. B. Matthews, J. R. May, J. M. Morgan, M. Newton, K. N. V. Palmer, P. B. Philip-Smith, D. A. Pond, P. D. G. Pugh, G. F. Roberts, J. Roche, B. Schofield, J. A. Shiers, J. F. N. Sidebotham, C. A. Storr, J. M. Stowers, M. Symons, R. G. Turner, D. R. D. Vanstone, B. H. Vawdrey, D. G. Veater, P. Venables, S. M. Vine, P. R. Westall, A. P. Wingate, L. Wolman, G. S. Yeoh. *Women:* R. C. A. Hunter, R. S. Mitchison, M. M. Tunstall-Behrens.

The Raymond Horton-Smith Prize for the academic year 1942–3 is not awarded.

The annual report of the Director of the Molteno Institute of Biology and Parasitology mentions that Prof. D. Keilin and Drs. E. F. Hartree, R. Hill, T. Mann, H. Laser, and M. F. Perutz have continued their work on the properties and function of intracellular catalysts and oxygen carriers. Dr. P. Tate continued to study the morphology and biology of Dipterous larvae; Dr. Ann Bishop has continued her work on the chemotherapy of avian malaria, on behalf of the Medical Research Council; Dr. Kenneth Smith and Mr. R. Markham have continued their studies on plant viruses, including new viruses attacking medicinal plants; and Dr. W. P. Rogers joined the Institute in October, 1942, to study the physiology and chemotherapy of parasitic nematodes.

## UNIVERSITY OF DURHAM

At a degree ceremony held in the Hall of the Castle at Durham on July 11 the Honorary D.C.L. of the University was conferred upon Dr. Gordon M. Holmes, F.R.S. In the course of his presentation speech the Public Orator recalled that Dr. Gordon Holmes graduated in arts and medicine at Trinity College, Dublin, and after post-graduate study abroad began his lifelong association with the National Hospital for Nervous Diseases, Queen Square. There he followed in the steps of distinguished teachers, and his wards in turn became the meeting-place of students from all parts of the world. To precision and clinical acumen he added an intimate knowledge of the work of others. His pre-eminence as a neurologist was recognized by his election as president of the Second International Congress of Neurology in 1935. He was for many years the indefatigable editor of *Brain*, and he maintained throughout life his interest in general medicine. In the last war Dr. Gordon Holmes was consulting neurologist to the B.E.F. in France; in the present war he served as chief consultant to the E.M.S. The University of Durham honoured him as a great teacher and as the leading representative to-day of the enduring English tradition of clinical neurology.

## UNIVERSITY OF GLASGOW

The degree of M.D. was conferred *in absentia* on Fl. Lieut. Nathan Sher, M.B., Ch.B., on July 22.

## UNIVERSITY OF ABERDEEN

At the Graduation Ceremony on June 29 Reginald Joseph Twort received the degree of M.D., with commendation for his thesis.

## UNIVERSITY OF WALES

### THE WELSH NATIONAL SCHOOL OF MEDICINE

The following candidates have satisfied the examiners at the examination indicated:

M.B., B.CH.—*Surgery:* Stuart Brest, L. G. G. Davies, E. M. L. Evans, Julia P. Gibbs, B. E. Heard, D. C. W. Jenkins, D. O. Lewis, Sarah M. Lewis, W. T. Lloyd, B. H. McCracken, Mary W. Owen, R. M. E. Seal, J. E. T. Sobey, †M. J. Tanner, J. W. Thomas, H. O. Williams, P. R. J. Williams, Winifred S. Williams.

† With distinction.

# Letters, Notes, and Answers

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 2111. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

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## ANY QUESTIONS?

### Some Points about Blood Transfusion

**Q.**—*(1) What is the total amount of blood in the body? (2) How much blood can a person lose in a single bleeding—e.g., from a war or air-raid wound—without loss of life? (3) How many pints of blood or other transfusion fluid can a patient be given with safety at one transfusion?*

**A.**—The total amount of blood in the body is in the neighbourhood of 11 pints. How much blood a person can lose in a single bleeding depends on the rate of loss. It is possible to lose a larger quantity if the loss is slow than if the loss is rapid. Again, there is a very great variation in the response of individuals to the loss of blood, and it would be difficult to give a categoric answer to the question, How much blood can a single person lose without loss of life? Probably if more than half the total blood is lost rapidly the outlook is not good. Again, the answer to the question, How many pints of blood or other transfusion fluid can a patient be given at one transfusion? is difficult. Experience in the present war has shown that no rule can be laid down as to dosage of transfusion fluids except to say that enough fluid must be given to raise the blood pressure to 100 mm. Hg and maintain it there. In one individual 1 pint may do this. In another it may require 6 pints or more. It is certainly safe to give as much as 2 pints in a quarter of an hour to a shocked individual, and this can then be followed by further amounts at a slower rate. Blood-pressure readings are essential in order to regulate dosage.

The above applies, of course, to traumatic injuries. The question of a sick person is very different. The sick individual often has cardiovascular system which is already damaged, and in such a case the rapid administration of large quantities of fluid is contra-indicated. Two to three pints given at a rate of 40 drops a minute is the largest amount one would probably give to a sick person who was not actually bleeding at the time of transfusion.

### Vaginal Pessary

**Q.**—*In your "Any Questions?" section of July 1 (p. 33) you state that the most efficient and least harmful vaginal pessary is one of phenyl mercuric acetate. Could you give me more information? I should also be glad of advice as to the most satisfactory mechanical contraceptive pessary for a normal vagina.*

**A.**—For further information regarding phenyl mercuric acetate the inquirer should refer to the article mentioned previously (*Lancet*, 1928, **2**, 882). Taking into consideration such factors as simplicity of application, harmlessness, and reasonable safety, the most satisfactory mechanical contraceptive for the average case is the Dutch cap vaginal diaphragm or pessary. The sizes vary from 50 to 90 mm. (diameter). It should fit the vaginal vault accurately, and this means a careful choice of size in each case. Moreover, it should not be used alone but in conjunction with a contraceptive paste or jelly. These appliances are supplied by most firms specializing in contraceptives, together with full instructions as to their use. An important point in technique is that the Dutch cap should not be removed until about eight hours after coitus.

### Parasympathomimetic Drugs

**Q.**—*When drugs such as carbachol, which act on the parasympathetic nervous system, are administered, is their effect equally great on all those parts supplied with parasympathetic nerves? Is the vasodilatation that follows administration evidence of the existence of vasodilator nerves of parasympathetic origin? Could you state briefly what are the main clinical indications for administering carbachol, and what are the risks attached to its use?*

**A.**—The intestine and the bladder appear to be particularly sensitive to carbachol (doryl); the heart and blood vessels to acetyl-methylcholine (mecholin). These differences in sensitivity of the different parts of the body are not very great and cannot result

demonstrated in experiments on animals. A clearer difference between these two drugs is that carbachol has nicotine actions on autonomic ganglia and that mecholin does not have these actions.

In practically all the places in the body where choline esters act there is a nerve which liberates a choline ester locally; but there is no logical necessity for the presence of such a nerve, and in a few places—e.g., the uterus of the young guinea-pig—there *is* no nerve. The argument which deduces the presence of a cholinergic nerve from the action of the drug is thus suggestive but not conclusive. The action of the drug gives no indication of the anatomical origin of the nerve. It is true that most cholinergic nerves are in the parasympathetic system, but the sympathetic system also contains many cholinergic nerves, and the nerves to voluntary muscle are cholinergic.

Carbachol has been successfully used in the treatment of post-operative intestinal atony, retention of urine, and glaucoma. In rheumatism, high blood pressure, and arterial spasm the results have been disappointing. Numerous effects of overdosage have been described, including headache, nausea, belching, peristaltic waves, colic, diarrhoea, flushing, asthma, a fall in blood pressure and in the pulse rate. Practically all these effects can be stopped with atropine in adequate doses. A valuable review of the actions of choline esters was written by F. R. Fraser in 1938 (*British Medical Journal*, **1**, 1249, 1293, and 1349).

### Liquid Paraffin

**Q.**—*There is difference of opinion as to the use of liquid paraffin internally. Some authorities describe it as a "non-irritating lubricant," while others condemn its use and suggest that it delays absorption of food and vitamins. It has even been suggested that it may cause irritation and lead to malignant changes in the gastro-intestinal tract. In twenty years of practice I have yet to confirm any of these pessimistic observations, but I should value an authoritative opinion on the subject.*

**A.**—There is good evidence that liquid paraffin can interfere with the absorption of carotene, vitamin D, calcium and phosphorus, and vitamin K. This may be specially important during pregnancy, and it has been suggested that whenever mineral oil is used cod-liver oil should also be given. It has also been suggested that the deleterious effect of liquid paraffin on absorption can be reduced by giving it as a single dose at night. There is some evidence that the prolonged administration of liquid paraffin may cause gastro-intestinal symptoms, accompanied by loss of weight in some cases, though this should not contraindicate its use as a laxative when given under medical supervision. It should not be used in salad dressings. There is no evidence that it may lead to malignant changes.

### Hypoproteinaemia

**Q.**—*If nutritional oedema is in part the result of hypoproteinaemia, there is presumably a stage where hypoproteinaemia exists before the oedema appears. Can hypoproteinaemia be exactly diagnosed by the biochemist? For this purpose is an estimation of the blood protein of clinical diagnostic value in suspected cases of under-nutrition?*

**A.**—Hypoproteinaemia, or an abnormal lowering of the plasma protein level, may be caused by insufficient protein intake due to undernutrition; faulty digestion of protein; inability to synthesize protein from amino-acids due to liver dysfunction; malignant disease; bowel obstruction; and increased protein loss through suppuration, ascites, nephrosis, burns, external gastro-intestinal fistulae, and haemorrhage.

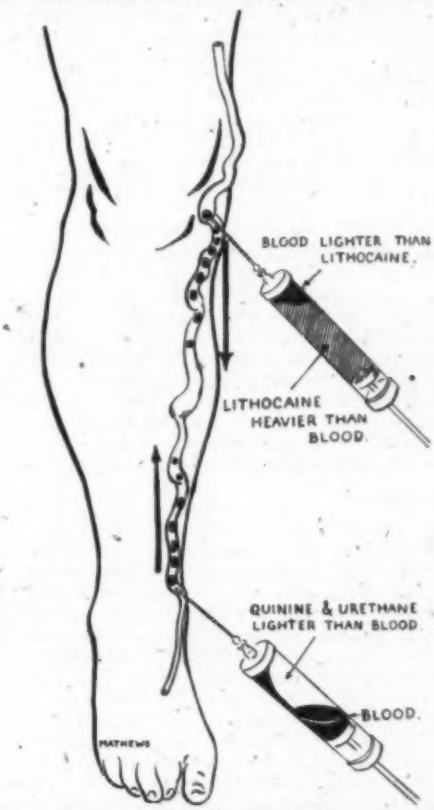
Hypoproteinaemia can be diagnosed by estimating the plasma proteins (for methods see *J. biol. Chem.*, 1936, **113**, 167; 1937, **119**, 481). The normal range is considered to be within 6.0 to 7.5 mg. per 100 c.cm. Values below 6.0 mg. are usually considered to indicate hypoproteinaemia, although Binkley (*Ann. Surg.*, 1943, **117**, 748) puts the figure at 6.5 mg. Many surgical patients have values between 6.0 and 4.5 mg. per 100 c.cm., and even 3.0 mg. has been recorded in cancer patients and in malnutrition. There are two pitfalls in the interpretation of the figures; a normal value may be found when actually the clinical manifestations of hypoproteinaemia may be present. The first pitfall is the effect of dehydration, which may increase the level of blood protein and so mask a true protein deficiency. The other pitfall is that the total protein (albumin and globulin) may be within normal limits, but the albumin fraction may be depleted. This is because the globulin fraction is sometimes increased, especially in severe infections, so that a fall in the albumin fraction is masked, unless separate estimations of albumin and globulin are carried out. The average figures for the plasma proteins are albumin 4.5%, globulin 2.0%. It is a fall in the plasma albumin that causes the clinical manifestations of hypoproteinaemia, since it is concerned mainly with the maintenance of fluid balance in the blood and tissues. To eliminate these pitfalls a red cell count or haematocrit determination should be carried out to see if there is any dehydration, and separate estimations of albumin and globulin should be made in doubtful cases. Some idea of the protein deficiency in the tissues can be gained if the plasma albumin and blood volume are known, because for every 1 g. of plasma albumin lost, 30 g. of protein are lost from the tissues. Thus if the plasma albumin is 3.0 g. % (average 4.5 g.) and the blood volume is 5 litres, the degree of protein depletion in the body is $\frac{(4.5-3.0)\times 5{,}000\times 30}{100\times 1{,}000}$ or 2.25 kilos. Such a figure is easily reached in patients suffering from cancer or starvation.

(For a full discussion of hypoproteinaemia see Elman and Lischer, *Internat. Abstract Surg.*, 1943, **76**, 533.)

### Twin Injections for Varicose Veins

**Q.**—*In using twin injections of quinine-urethane and lithium salicylate for varicose veins, does it matter in which order these solutions are used, and if so, why?*

**A.**—No, the order does not matter, but the level at which they are injected is significant. Quinine and urethane is lighter than blood and therefore should be injected at the lower end of the length of vein it is desired to thrombose. Lithium salicylate is heavier than blood and is therefore injected at the upper end of the




vein requiring to be sclerosed. The two substances meet in the vein and form a sticky precipitate with a powerful sclerosing action. Quinine diffuses up the vein, the lithocaine gravitates it down; they are both sclerosing in their actions individually and their power is enhanced when being used together in this way. I enclose a diagram illustrating this.

### Hay-fever

**Q.**—*In the second week of July a girl aged 10 was playing in some long, overgrown grass, and within half an hour of this developed urticarial patches on the back and considerable oedema of both eyelids, the eyes being almost closed as a result. The conjunctivae were slightly injected. There was no accompanying "hay-fever." Was this an allergic reaction to Timothy-grass pollen? What was the path of entry of the offending protein, and would there be any point in trying to desensitize?*

**A.**—Quite a number of children develop ocular symptoms as the first sign of hay-fever. They roll in the grass; some of the pollen gets in their eyes and sets up a mild irritation. They then rub their eyes, and their hands are usually covered with pollen from pulling and handling the grass; this sets up an angioneurotic oedema of the eyelids from friction and local absorption. It is quite likely there was some accompanying urticaria of the nasal mucous membrane, but the usual objective symptoms of sneezing and running were not present. This is a pollen sensitivity probably to several of the English grasses (not necessarily Timothy), and the child should be tested with the various English grasses and a course of desensitizing injections given weekly from the first week in January until the first week in June next year.

### Skin Testing by Dust Extract

**Q.**—*A book on allergy recommends skin testing by the dust of the asthmatic patient's own house. Please tell me if (and how) this is sterilized or treated before applying to the scratch, and how it is collected.*

**A.**—Dust extract is prepared, if possible, from the contents of the vacuum cleaner applied particularly to mattresses and upholstered furniture rather than to carpets and rugs, as ordinary street dust is relatively inert. The dust is first defatted with ether, and each 25 g. of the dried defatted dust is covered with 100 ml. of Coca's solution (an antiseptic specially buffered saline solution, *p*H 7.0) and allowed to stand for 24 hours. The solution is filtered first through paper to clear it; and then through a Seitz filter to render it bacterium-free, as heat sterilization would tend to destroy its allergic properties. For a scratch test the resulting fluid may be used, but for intradermal testing it should be diluted 1 : 100. Coca's solution is used as a control.

### Motility of Spermatozoa

**Q.**—*A man aged 38, married 10 years, is anxious to have children. His wife is aged 36. Both have recently been examined by a competent gynaecologist and urologist respectively. The spermatozoa of the husband were found to be non-motile, and therefore presumably dead. The patient was advised to have injections of chorionic gonadotrophin and of follicle-stimulating hormone. (1) What effect, if any, are these substances likely to have on the non-motile spermatozoa? (2) If the effect of the hormones is to cause increased motility, will this persist as a permanent feature, or will retrogression take place after stopping the injections? (3) Should he have his wife with him while undergoing the treatment? (4) Can I give him any guarantee that the treatment will be successful?*

**A.**—The absence of motility in a specimen which has not been obtained in the consulting-room without contact with rubber, and which has not been examined immediately, is of questionable significance. On several occasions I have found motile spermatozoa on direct examination in patients who believed their spermatozoa to be non-motile as the result of a laboratory report on a transported specimen, even when transferred from a condom to a glass tube. Non-motility by itself is rarely present in the absence of other abnormal features. For the purpose of answering this question, I will assume that the number of spermatozoa was considerably reduced, and that there were many pathologically shaped, as well as a high percentage of non-motile, spermatozoa. Theoretically (1) chorionic gonadotrophins should stimulate interstitial cells, whereas (2) follicle-stimulating hormone, obtained from pregnant mares' serum, should stimulate seminiferous tubules. In actual practice the first appears to work in this respect in cases of hypogonadism secondary to pituitary hypofunction, and successful results are manifested by the return of libido and erections. As regards the second, there is little or no evidence that these gonadotrophins affect the seminiferous tubules in man, or appreciably influence the character of the spermatic fluid and its contents. Certainly any effects obtained by gonadotrophic stimuli tend to retrogression after stopping the therapy. (3) As to the presence of the wife, obviously this is a necessary link in any therapy designed to produce pregnancy, but coitus is not essential for a gonadotrophic stimulus to be effective. (4) From what has been written above, it is obvious that no guarantee can be given as to the success of the treatment.

### Brittle Nails after Gastrectomy

**Q.**—*What are the cause and treatment of brittle finger-nails with many longitudinal cracks? The patient, a woman of 58, had a partial gastrectomy 10 years ago, and another gastrectomy for recurrent anastomotic ulcer 3 years ago; so that only a small portion of her stomach remains. It is only since this later operation that she has complained of the brittle cracking nails. Her nails are otherwise normal in shape (not spoon-shaped or hollow). She has no indigestion and lives on a normal mixed diet; her health is good. Her blood count is: R.B.C. 5,000,000 per c.mm.; Hb 86%; C.I. 86; W.B.C. 7,600 per c.mm. Differential: polymorphs 63%, lmyphocytes 32%, large monocytes 3%, basophils nil, eosinophils 2%. R.B.C. slightly hypochromic; no abnormalities of shape or size; no nucleated R.B.C.*

**A.**—Brittle finger-nails are not uncommon in women past middle age, particularly in time of war when additional housework increases the wear and tear on the nails. Moreover, the fat-soluble vitamins are believed to promote the health of the nails, and these principles may be reduced in the wartime diet.[2] It is therefore not certain that the gastrectomy is the sole cause of the brittle nails, though it may well have played the chief part by impairing the absorption of the food. Iron deficiency is unlikely to be a factor, in view of the absence of anaemia and koilonychia, but calcium and fats may be lacking. These faults should be repaired by the two pints of milk a day to which this patient is entitled by her gastrectomy; this puts her into Class I (*f*) in the schedule of conditions qualifying for priority claims on liquid milk. Another reason why milk should be beneficial is that the milk protein supplies organic sulphur, which is an important constituent of the nails. Nail-polish, polish-remover and anti-cuticle solutions should be rigorously barred and a simple cream applied to the nails. Hypothyroidism must not be overlooked.

## LETTERS, NOTES, ETC.

### Stubborn Asthma

Dr. A. H. DOUTHWAITE (London) writes: It may be helpful to your correspondent who raised this subject under "Any Questions?" (July 22, p. 135), to receive a suggestion that he try pethidine 100 mg. subcutaneously, if the measures which have been advocated fail. It has none of the alarming effects of morphine, which is most dangerous in asthma. Status asthmaticus I have found to be promptly terminated by it when continuous adrenaline treatment has failed.

### Artificial Insemination

A correspondent writes: Your reply concerning facilities for artificial insemination in this country (July 8, p. 65) is not strictly accurate. This method of treating sterility has for some time been employed in suitable cases at the Exeter clinic of the Family Planning Association.

### Unusual Ear Conditions

Dr. S. L. ISAACS (Merthyr Tydfil) writes: I was interested in the letter of Mr. C. Hamblen-Thomas concerning large perforations due to glycerin of carbolic drops. I have found on numerous occasions that patients are in the habit of warming these drops by placing the bottle *with the cork removed* in about half a cupful of hot water, with the result that after standing in this position the vapour over and above the exposed glycerin acid carbolic is quickly absorbed by the glycerin (glycerin, of course, being very hygroscopic), with the obvious result that a caustic effect is produced by the addition of the water to the glycerin acid carbolic.

### Clinical View of Shock

Dr. W. W. WALTHER (Queen Mary's Hospital for the East End) writes: Dr. Horace Hill (July 22, p. 126) should think again. The symptoms of shock are not identical with those occurring after the injection of histamine. As Mr. Zachary Cope points out, "the skin is usually cold and pale or cyanotic," and there is no flushing as shown by histamine.

### High Birth Weights

Fl. Lieut. K. M. FOX, R.A.F., writes from India: Further to the question on high birth weights in your issue of April 8 (p. 510), which has just arrived in this country, it might interest your correspondent to know that in the summer of 1938 I was called in to attend a patient by a midwife who had made a provisional diagnosis of locked twins. However, bimanual examination soon showed that there were triplets, not twins, with the leading member of the trio presenting a large head at the os. Under anaesthesia the patient was delivered of triplets, the first two each weighing 6½ lb., and the third one a mere 5½ lb., total weight 18½ lb. Each child sucked the breast and made uneventful progress.

### Trichomonas and Vaginal Discharge

Dr. W. N. MASCALL (acting director, L.C.C. (Whitechapel) Clinic) writes: I read in the *Journal* of July 22 under the heading "Vaginal Discharge after Hysterectomy" on page 135 the following sentence: "If both ovaries were removed it is possible that a trichomonas infection has been lighted up." I would like to point out that trichomonas infestation of the vagina is extremely rare either before puberty or after the menopause, whether this is natural or artificial. The average *p*H of the vagina is 7 at these times owing to the low glycogen content of the vaginal epithelium. The presence of glycogen is essential for the survival of the trichomonads, and it is believed the ovarian activity is essential for maintaining the necessary level in the vaginal epithelium. In adults the production of lactic acid from the glycogen by the action of Döderlein's bacillus maintains the vaginal acidity at *p*H 5 to 6. At this degree of acidity the *Trichomonas vaginalis* flourishes.

### Offers of Hospitality for Doctors' Children

The following further offers to accommodate the children of doctors practising in dangerous areas have been received. Dr. F., who practises in a rural area in Dorset, would take one child, and suggests that a girl between the ages of 3 and 5 would be best as he himself has a daughter of 4. There are no educational facilities in the district apart from the local elementary school. Dr. G. offers hospitality in the Isle of Man to a mother and child or to two children. If the former, help in the house would be expected, but there would be no financial expense except the cost of the journey. Any readers interested in these offers may communicate with the Secretary at B.M.A. House, Tavistock Square, W.C.1.